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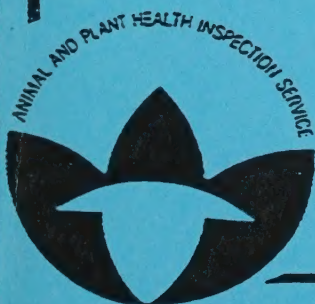
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Antimicrobial Resistance Issues In Animal Agriculture



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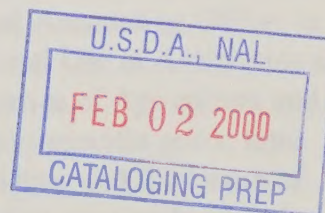
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Antimicrobial Resistance Issues In Animal Agriculture

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Introduction

During the past decade, the threat of antimicrobial resistance has become increasingly real and its global dimensions have been increasingly recognized. Antimicrobial resistance is defined as a property of bacteria that confers the capacity to inactivate or exclude antibiotics, or a mechanism that blocks the inhibitory or killing effects of antibiotics, leading to survival despite exposure to antimicrobials (Institute of Medicine, 1998). Some bacteria become multi-resistant, i.e., resistant to different groups of antibiotics. Increasing reports of outbreaks of antimicrobial resistant bacteria, such as hospital outbreaks of vancomycin resistant enterococci (VRE), community outbreaks of antimicrobial resistant *Streptococcus pneumoniae* (Tenover, 1996) and human and animal outbreaks of multi-resistant *Salmonella* Typhimurium definitive type 104 (DT104) (Akkina et al., 1999), have heightened the concerns of the international public- and animal-health communities, medical and veterinary clinicians and the general public. Another reason for increased concern is the slowing of research and development of new antimicrobials due to the cost and time to develop new drugs as well as a focus by pharmaceutical companies on developing products for non-infectious disease.

Antimicrobial resistance issues have the potential to impact animal agriculture in a number of ways. Concern about the role of animal agriculture in antimicrobial resistance development and spread has recently prompted the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM), to propose a new "Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals", which may lead to new regulations on the approval process of antimicrobials for use in food-producing animals. In addition, the Center for Science in the Public Interest (CSPI) and other groups are petitioning the FDA to ban subtherapeutic or growth promotant use of antimicrobials that are currently used, or that may be used in the future for humans. In the European Union (EU), four antimicrobials (bacitracin zinc, spiramycin, virginiamycin and tylosin phosphate) which are considered important in treating humans were banned for use in animal feed, effective July 1, 1999. Controversy over antimicrobial resistant pathogens and use of antimicrobials in food animals could impact future trade decisions.

One of the USDA/APHIS/Veterinary Services (VS) strategic principles for behavior and action outlined in the VS Strategic Plan, FY2000/2002, is to use its resources and act together with other partner agencies and the public to address food safety, public health, and natural resource issues of overlapping knowledge and concern. The issue of antimicrobial resistance is a good example of how the interaction of animal and human populations, and the environment, has become more complex and requires multidisciplinary attention and coordination from the public- and animal- health and agricultural sectors. The United States General Accounting Office, in their recent report (GAO/RCED-99-74) titled "Food Safety: The Agricultural Use of Antibiotics and Its Implication for Human Health", has recommended that the Secretaries of Agriculture and Health and Human Services develop and implement a plan that contains specific goals, time frames, and resources needed to evaluate the risks and benefits of existing and future use of antimicrobials in agriculture, including identifying and filling critical data gaps and research needs. A coordinated effort between USDA, FDA, producers, practitioners and the pharmaceutical industry can assist in providing the scientific information needed to determine the prevalence and

trends of antimicrobial resistance on the farm, identify risk factors for resistance development, develop and implement interventions to reduce antimicrobial resistance, and evaluate the effectiveness of interventions.

Objective

The purpose of this series of papers is to assist VS decision-makers in setting priorities and allocating resources for activities and research to address this threat to animal and public health, and to provide a knowledge base in antimicrobial resistance for VS personnel who want to educate themselves about antimicrobial drug resistance issues in animal agriculture. Although the document may benefit significantly a variety of readers, it is not intended for those who consider themselves, or are considered by others, to be experts in antimicrobial resistance issues. Nor is the document intended for those readers who do not have a basic background in veterinary medicine, epidemiology, microbiology, livestock production medicine, and related areas.

Background

An antimicrobial is an agent that kills bacteria or suppresses their multiplication or growth. Fleming discovered penicillin in 1928 and soon after other classes of antimicrobials were also identified. The first therapeutic use of penicillin however was not until 1940. Consequently, for more than 50 years the world has enjoyed a tremendous decrease in mortality and morbidity from bacterial diseases. Existence of resistance to antimicrobials was realized early. Also in 1940, Abraham and Chain described penicillinase, an enzyme that inactivates penicillin, in *Escherichia coli* (Tenover, 1996). The intrinsic ability of some organisms to resist antimicrobials was clearly present prior to the clinical use of antimicrobials. In addition, antimicrobial resistance can occur as a result of random genetic mutations in bacteria, leading to variation in susceptibility within any bacterial population. More commonly, resistance is not due to a chromosomal change event, but to the presence of extrachromosomal DNA (plasmid) which was acquired from another bacteria. Use of antimicrobials however, selects for these resistant organisms, leaving them to multiply more freely after the susceptible bacteria have been eliminated. This phenomenon is called selective pressure.

Antibiotic resistance is a complex global issue that should not be over simplified or over generalized. For example, antibiotic resistance does not always follow antibiotic use.

Streptococcus pyogenes remains fully sensitive to penicillin despite selective pressure (Phillips, 1998). Conversely, the removal of selective pressure does not always lead to reversal of resistance. An example of this is the occurrence of chloramphenicol-resistant *E. coli* many years after chloramphenicol ceased to be used in Britain (Phillips, 1998). The presence or absence of resistance applies for a specific microbial isolate in relation to one or more specific antimicrobial(s), and therefore is often geographically specific as well. It is not only resistant pathogens that are of concern. Resistance factors (genes) present in commensal (non-pathogenic) intestinal bacteria can be transferred to pathogenic bacteria.

The development of a resistant microorganism and its subsequent transmission in the human or animal population is often a multifactorial and multistep process. One major factor in the

increasing problem of resistance in human pathogens is the overuse and injudicious use of antimicrobials in the hospital and community environments. There is also concern that antimicrobial use in food animals can lead to the selection of antimicrobial resistant zoonotic enteric pathogens which may then be transferred to people by the consumption of contaminated food or by direct animal contact. Though instances of resistance transfer, either direct or indirect, from animals to humans have been described, (Wegener et al., 1999; Spika et al., 1987; Institute of Medicine, 1998), the true magnitude of the medical impact from antimicrobial resistant bacteria originating from food animals or companion animals (pets and horses), is mostly unknown. Many reviews are available in the literature regarding the relationship between antibiotic resistance in humans and resistance in animals, with the conclusions varying widely from minimal impact to a substantial impact (Threlfall et al., 1992; Shah, 1993; Wiedmann, 1993; National Research Council, 1999). Another concern is resistant bacteria excreted in the feces of animals who have received antimicrobials, which contributes to the reservoir of resistant bacteria in the environment (Levy, 1998; National Research Council, 1999). Antimicrobials are used in plant agriculture and in aquaculture to destroy and prevent fungal and bacterial pests. This use may also contribute to the environmental reservoir of resistant microbes. In addition, the contribution of companion animals, i.e., pets and horses, to resistance in humans is unknown.

There are many other factors which contribute to the rising incidence of resistance in human pathogens. These factors include liberal availability of antimicrobials in some countries and societal factors such as the increasing number of immunocompromised individuals, unnecessary antimicrobial use caused by patient demands for antimicrobial treatment of viral infections, the changing population age structure, and an increase in institutional care environments such as day care centers, nursing homes and hospitals (Livermore, 1998). In these environments large numbers of susceptible persons in close contact, and with high incidence of antibiotic use, promote transmission of resistant microbes and/or factors. Similarly in animal agriculture, the current trend in developed countries toward more concentrated livestock production, with fewer farms and more animals per farm, places large numbers of susceptible animals in close physical contact. In addition, increasing international travel and trade allows resistant organisms to quickly disseminate globally.

Implications of Antimicrobial Resistance for Human Health

Antimicrobial resistant infections in humans lead to increased morbidity, mortality, and longer hospitalizations. Increased health care costs are associated particularly with longer hospital stays and use of more expensive antimicrobials necessary to fight resistant pathogens. Often the antimicrobials used to combat resistant organisms are more toxic, with more serious side effects. Other associated costs to society include lost work days and value of lives lost due to deaths.

The cost of antimicrobial resistant hospital acquired infections was estimated by the National Foundation for Infectious Disease to be as high as four billion dollars annually. In 1995, the Office of Technology Assessment (OTA) produced a minimum estimate of 1.3 billion (1992 dollars) yearly in-hospital costs related specifically to six species of antibiotic resistant bacteria and only one antibiotic (Institute of Medicine, 1998).

Antimicrobial Use in Animal Agriculture

Antimicrobials are used in animal agriculture to improve:

- 1) the health and welfare of the animal, through treatment of disease
- 2) carcass quality
- 3) the economic efficiency of growth and production
- 4) public health, through decreased shedding of zoonotic pathogens which may contaminate both the environment and food animal products (National Research Council, 1999).

Clearly, the use of antimicrobials in animal agriculture has many important benefits.

Antimicrobials are an integral component in the treatment of livestock disease and in livestock production in the U.S. The loss of efficacious antimicrobials, either due to development of resistance or due to limiting availability or use, could potentially have serious consequences. Consequences include areas such as changes in the makeup of the food supply, food cost changes, impacts on producers, impacts on animals, and overall impacts on food quality.

Actions by the public- and animal- health communities to manage antimicrobial resistance must be based on sound science. The following series of reports provide a brief review of some of the scientific aspects of antimicrobial resistance issues and animal agriculture.

Executive Summaries

Understanding the Biology of Antimicrobial Resistance

Summary

To make science-based decisions about priorities, activities, and resource allocation to address the issue of antimicrobial resistance, a working knowledge of the biology of resistance is necessary. This section reviews the basics of antimicrobial mechanisms of action and the development and spread of microbial mechanisms to resist antibiotics. Antimicrobial susceptibility testing of microbial isolates is an important tool for clinical use and for monitoring the prevalence of antimicrobial resistance. The broth microdilution method and the disk diffusion method are described and discussed.

Antibiotic Use in U.S. Livestock Production

Summary

Antibiotics are used in livestock production as therapeutics, prophylactics, and growth promoters. These drugs assist in sustaining livestock production and in controlling bacterial pathogens that may be transferred to humans. The scientific community is increasingly concerned about the

transfer of antibiotic resistance and/or antibiotic resistance determinants from animals to humans. These concerns may lead to increased restrictions on the use of antibiotics in animal agriculture as well as to decreased exports. This report lists many of the antibiotics approved for use in livestock production in the U.S., the EU, and the UK. The report also describes the purposes and prevalence of antibiotic use in the U.S. livestock population, based on several different studies by the National Animal Health Monitoring System (NAHMS) between 1990 and 1997. Antibiotics were used in most phases of swine production and were administered via injection, feed, water and orally. Antibiotic use increased in swine production between 1990 and 1995. Approximately 25 percent of small cattle feedlot operations and 70 percent of large feedlot operations used antibiotics. Similarly, approximately 31 percent of cattle on small feedlot operations and 57 percent of cattle on large feedlot operations were exposed to antibiotics. Tetracycline and derivatives of tetracycline were some of the most frequently used in-feed additives on feedlot operations. Varying percentages of dairy operations and varying percentages of dairy cows on these operations were exposed to antibiotics during lactation and the dry period. Only a few antibiotics have been approved for use in catfish production. Romet was used to manage enteric septicemia of catfish on 41 percent of affected operations. Increased restrictions on the use of antibiotics could have significant implications for animal health. Therefore, developing economically feasible, chemotherapeutic and non-chemotherapeutic alternatives to antibiotics (e.g., management strategies) may become vital to maintain the health of U.S. livestock and to maintain viable export markets.

Prevalence of *Salmonella* and *Escherichia coli* On U.S. Livestock Operations

Summary

Salmonella and *Escherichia coli* (*E. coli*) cause significant morbidity and mortality in livestock and therefore are two of the most economically significant pathogens of livestock. In humans, *Salmonella* and *E. coli* are important causes of food-borne illness. The Centers for Disease Control and Prevention (CDC) estimates 1.4 million *Salmonella* cases with 600 deaths occur each year. Morbidity and mortality from *Salmonella* leads to significant economic loss to the population through medical expenses and productivity lost. Since antimicrobials are used in livestock to control these two pathogens, there is concern about antibiotic resistance development in these pathogens and subsequent transfer to humans through contaminated food. The prevalence of these two pathogens in livestock therefore may impact the level of antibiotic use, antibiotic resistance development and human food-borne disease. This concern provides impetus for thoroughly understanding the ecology and epidemiology of *Salmonella* and *E. coli* infections in animals.

The objective of this report is to provide an abbreviated review of *Salmonella* and *E. coli* infections, and present the descriptive results of several national studies by the USDA's National Animal Health Monitoring System (NAHMS) of *Salmonella* and *E. coli* on U.S. livestock operations. *Salmonella* were found in animals on dairy, feedlot cattle, and swine operations. None of the *Salmonella* serotypes from feedlot cattle were on the CDC's list of the top 5

Salmonella isolates from humans in 1991. However, three of the serotypes from swine were on the CDC's list of the top 5 *Salmonella* isolates from humans in 1994. *E. coli* O157:H7 was detected in dairy calves and feedlot cattle, but the prevalence generally was low in comparison to the prevalence of some other pathogens. *E. coli* O157:H7 was not found in a 1995 survey of U.S. swine operations. Diseases in swine that may be caused by other serotypes of *E. coli* were reported to have been an important cause of morbidity and mortality on swine operations.

Epidemiology of Antimicrobial Resistance in *Salmonella* , *Escherichia coli* And Other Selected Pathogens in Livestock

Summary

This report summarizes the descriptive epidemiology of antimicrobial resistance in animals in different countries, as presented at the WHO conference on "The Medical Impact of the Use of Antimicrobials in Food Animals" in October, 1997 (World Health Organization, 1998). This brief description of the epidemiology of antimicrobial resistance in livestock focuses primarily on two important zoonotic pathogens, *Salmonella* and *Escherichia coli*. In addition, the epidemiology of antimicrobial resistance in livestock is discussed briefly for the following pathogens: *Staphylococcus aureus*, *Serpulina hyodysenteriae*, *Campylobacter*, *Salmonella* Typhimurium DT104, and respiratory pathogens. Finally, resistance to several antimicrobials including vancomycin, streptogramins, and quinolones, is discussed.

Widespread resistance to old and recently developed antimicrobial drugs is occurring in several pathogens that are commonly associated with diseases in animals and humans. In general, long-term trends in the prevalences of resistance were not available from many countries because many surveillance systems were organized only recently. Where available, data indicates that the prevalence of resistance of some infectious agents in animals to some antimicrobial drugs used in livestock production is increasing, and it is already high in some situations.

Strategies to Reduce Antimicrobial Resistance in Food Animal Agriculture

Summary

Limiting availability of antimicrobials, enhanced surveillance, and on-farm interventions (including prudent antimicrobial use and management practices) have been proposed as key strategies to reduce antimicrobial resistance in food animal agriculture. Improved, rapid diagnostic methods and accelerated development and approval of new antimicrobial drugs can also play an important role in preventing and controlling antimicrobial resistance. This report describes the essential characteristics of a surveillance system for antimicrobial resistance and briefly reviews recently organized surveillance systems in the U.S., France, and Sweden. In addition, management practices that can decrease the need for antimicrobial use on the farm are explored. Examples of management practices that decrease the need for antimicrobials are the use of vaccines, probiotics, immune enhancers, good husbandry practices, and biosecurity. According to data from the

USDA's National Animal Health Monitoring System (NAHMS), appropriate use of health management practices could be pivotal to an on-farm intervention strategy to reduce antimicrobial resistance on U.S. swine, dairy, and beef operations. Some specific results of NAHMS' health management data were: (1) Only 32% of calves received the recommended volume of colostrum during the first feeding. (2) The immunoglobulin concentration was less than ideal in approximately 67% of the 2,177 dairy calves sampled. (3) Proper protection against respiratory pathogens may have been inadequate in as many as 86% of beef calves in the U.S. at the time of sale in 1997, based on the frequency of vaccination. Educating animal producers and veterinarians concerning these strategies to prevent and control antimicrobial resistance is essential to their success.

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Understanding the Biology of Antimicrobial Resistance

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Summary

To make science-based decisions about priorities, activities, and resource allocation to address the issue of antimicrobial resistance, a working knowledge of the biology of resistance is necessary. This section will review the basics of antimicrobial mechanisms of action and the development and spread of microbial mechanisms to resist antibiotics. Antimicrobial susceptibility testing of microbial isolates is an important tool for clinical use and for monitoring the prevalence of antimicrobial resistance. The broth microdilution method and the disk diffusion method are described and discussed.

Antimicrobial Classification and Mechanisms of Action

To understand how antimicrobial resistance occurs at the cellular level, it helps to review the various types of antimicrobials and their mechanisms of action. Antibacterials can be classified by biochemical structure and by mechanism of action. The major biochemical classes are beta-lactams, macrolides, aminoglycosides, tetracyclines, glycopeptides, sulfonamides, and quinolones. The major mechanisms of action of systemic antimicrobials involve inhibition of the following processes which are essential for bacterial growth and/or division: cell wall synthesis, nucleic acid replication, protein synthesis, and folate metabolism (Neu et al., 1996).

Inhibition of Cell Wall Synthesis

An essential component of the bacterial cell wall is a specific mucopeptide called a peptidoglycan. Multiple enzymes are required for peptidoglycan synthesis and attachment to the cell wall. Enzymes involved in the final stage of cell wall synthesis are called transpeptidases. Beta-lactam antimicrobials (penicillins, cephalosporins, carbapenems, monobactams) bind to transpeptidases and inhibit peptidoglycan formation, thus interfering with cell wall synthesis. These transpeptidase enzymes and some other bacterial proteins to which penicillins bind, are collectively called penicillin-binding proteins (PBPs). The PBPs are different for Gram-positive and Gram-negative bacteria and in anaerobic species. Beta-lactams are only efficacious against actively dividing bacteria, since that is when a new cell wall is being created.

Vancomycin is an example of a glycopeptide antimicrobial which also interferes with cell wall synthesis. It interrupts cell wall synthesis by forming a complex with residues of peptidoglycan precursors. Vancomycin and other glycopeptides also inhibit biochemical reactions in the cell wall catalyzed by transpeptidases and D,D-carboxypeptidases. Vancomycin has a large and complex chemical structure, and therefore is unable to penetrate the outer membrane of Gram-negative organisms. Beta-lactams and vancomycin, whose active site is the cell wall, can act synergistically with an aminoglycoside antimicrobial against enterococci. The cell wall active agents puncture the cell wall, allowing the aminoglycoside to get through the cytoplasm to reach its active target site, the ribosome.

Inhibition of Nucleic Acid (DNA) Replication

DNA gyrase is an enzyme that controls the folding or supercoiling of the DNA during DNA replication. It is essential for preventing the DNA molecule from becoming entangled during replication of circular chromosomes in bacteria. The quinolone class of antimicrobials bind to the DNA molecule-gyrase complex, inhibiting its function and leading to bacterial cell death. The original quinolone was naladixic acid, which only acts on aerobic Gram-negative species. The newer fluoroquinolones, such as ciprofloxacin, norfloxacin, and ofloxacin, have a much broader spectrum of activity.

Inhibition of Protein Synthesis

By interfering with protein synthesis taking place in the ribosome, several classes of antimicrobials are able to stop cell division. Bacterial ribosomes contain two subunits, the 50S and 30S subunits. Certain antimicrobials bind to one or both subunits, and cause misreading of the genetic code or formation of abnormal, nonfunctional protein complexes. Aminoglycosides (gentamicin, tobramycin, amikacin, streptomycin) act primarily by binding to the 30S subunit. Tetracyclines are another biochemical class of antibiotic which also bind to the 30S ribosome. Tetracyclines are bacteriostatic rather than bactericidal, because their binding to the ribosome is transient. Several classes of antimicrobials inhibit the 50S ribosomal subunit. Macrolides (erythromycin), chloramphenicol and clindamycin are primarily bacteriostatic and attach reversibly to the 50S subunit and interfere with the linking of amino acids.

Inhibition of Folate Metabolism

Bacteria usually lack the ability to take up folic acid from the environment and must synthesize it internally. Trimethoprim and the sulfonamides interfere with folate metabolism by competitively blocking the synthesis of tetrahydrofolate. Trimethoprim and sulfonamides are usually administered together because trimethoprim potentiates sulfonamides.

Development and Spread of Mechanisms of Antimicrobial Resistance

There are two main aspects to the biology of antimicrobial resistance. One is concerned with the development, acquisition and spread of the resistance gene or factor itself. The other is the specific biochemical mechanism conveyed by this resistance gene or factor which thwarts the antimicrobial attack.

Resistance can be an intrinsic property of the bacteria itself which is possessed by all members of the genus, and renders it unaffected by a specific mechanism of an antimicrobial. Resistance can also develop as the result of a single or multiple step mutation, for example, which changes a ribosomal protein that was a target of an aminoglycoside antimicrobial. More commonly, resistance is not due to a chromosomal change event, but to the presence of extrachromosomal DNA which was acquired from another bacteria. This type of resistance is called plasmid-mediated (Neu et al., 1996). Bacteria can transfer chromosomal or plasmid DNA-containing resistance genes to another bacteria by conjugation, transduction, and transformation.

A plasmid is a circular body of doublestranded DNA which is separate from the chromosome and carries genes that encode various traits such as virulence and antimicrobial resistance (Fraimow et al., 1995). There are two types of plasmids based on their ability to transfer from one bacterium to another. Conjugative plasmids can transfer to other bacteria via sex pili, and nonconjugative plasmids cannot. Cell-to-cell contact is necessary for conjugation to occur and both donor and recipient end up with a copy of the plasmid. R-factors are plasmids that have traits for both conjugation and antimicrobial resistance (McManus, 1997). The transfer of plasmids by conjugation is an extremely important mechanism because transfer can occur in a broad range of bacterial species and can extend to highly unrelated organisms. A single plasmid can contain genes conferring resistance to multiple classes of antimicrobials.

Transduction occurs when chromosomal or plasmid DNA is transferred from one bacterium to another by bacteriophages (McManus, 1997). Bacteriophages are viruses that attack bacteria. Since bacteriophages have a very narrow host range, this is a less important method of resistance gene transfer.

Bacteria can pick up free or “naked” DNA from their environment by a process called transformation. The presence of free DNA is common after cell lysis, but the range of compatibility between the free DNA and the intact recipient bacteria is narrow (McManus, 1997). Therefore, transformation is not an important method of resistance gene transfer.

A transposon is a gene which contains an insertion sequence at each end. The insertion sequences allow the gene to jump to different locations on chromosomal DNA, from plasmid to plasmid or from chromosome to plasmid (McManus, 1997). The movement of a transposon is called transposition. Transposons are important because they can move resistance genes from a nonconjugative plasmid or chromosome to a conjugative plasmid, which can then be easily transferred to other bacteria. Another genetic element, called an integron, may be located on a plasmid or transposon. An integron contains one or more resistance genes (called gene cassettes) between two conserved DNA regions.

Biochemical Mechanisms of Bacterial Antimicrobial Resistance

There are four basic biochemical mechanisms by which bacteria resist the killing effects of antimicrobials: 1) alteration of the antimicrobial's target receptor molecule in the bacteria, 2) decreasing the assessibility of the antimicrobial to the target by altering entry of the antimicrobial into the cell or increasing removal of the antimicrobial from the cell, 3) destruction or inactivation of the antimicrobial, and 4) synthesis by the bacteria of a new metabolic pathway that is not inhibited by the antimicrobial (Neu et al., 1996). Resistance in bacteria arises through a multistep process, from low level to high level, unless a plasmid is acquired which already contains genes for full blown resistance (Levy, 1998). Multiple mechanisms of resistance can occur in a single isolate, leading to higher levels of resistance (Hawkey, 1998). Mechanisms of resistance are often specific to a particular antimicrobial agent in relation to a specific bacterial species, as the examples below will illustrate, and should not be generalized. A specific resistance mechanism operating in a specific bacterial species may also be a geographically local phenomenon.

Alteration of the Target Receptor

By altering the target receptor molecule, the antimicrobial is unable to bind and therefore does not have any effect. Altered penicillin-binding proteins (PBPs) are the cause of resistance in certain *Streptococcus pneumoniae* strains to penicillin G and also explain resistance of certain strains of *Staphylococcus aureus* to beta-lactamase stable penicillins. Resistance to fluoroquinolones is frequently associated with mutations in DNA gyrase, the target molecule, and therefore inhibit binding (Jenkins, 1996). Macrolide-lincomycin resistance in clinical isolates of staphylococci and streptococci is due to a biochemical change (methylation) in the 50S ribosomal subunit RNA, which decreases binding. The gene which causes this change in the ribosomal RNA is plasmid mediated and encoded on transposons.

Decreased accessibility of the antimicrobial agent to the target site can be accomplished in a number of ways. Membrane characteristics can inhibit the antimicrobial from crossing the membrane and entering the cell (decreased uptake), or the antimicrobial can be altered in its passage across the membrane so it can't bind its target. Resistant bacteria can also actively remove the antimicrobial from the cell (increased efflux). Tetracycline resistance is due to a decrease in the levels of drug accumulation caused by decreased uptake and increased efflux. This resistance is usually plasmid-mediated. Plasmids containing tetracycline resistance move among members of the Enterobacteriaceae, and also have moved between *S. Aureus*, *S. epidermidis*, *S. pyogenes*, *S. pneumoniae* and *S. faecalis*. Aminoglycoside resistance is largely due to the alteration of the compound in the periplasmic space by bacterial enzymes that acetylate, phosphorylate or adenylate aminoglycosides. This alteration of the compound leads to binding to the bacterial ribosomes and poor uptake into the cell. The genes coding for aminoglycoside altering enzymes are often found on transposons and have been identified in members of the Enterobacteriaceae and *P. aeruginosa*, *S. pneumoniae* and Gram-positive species such as *S. aureus*, *S. faecalis*, and *S. pyogenes* (Neu et al., 1996).

Destruction or Inactivation of the Antimicrobial

This resistance mechanism usually involves the hyperproduction of an enzyme that inactivates the drug. The most well-known example are the beta-lactamases, which are found in both Gram-negative and Gram-positive species. The clinically relevant Gram-positive bacteria that produce beta-lactamases are staphylococci and enterococci. Beta-lactamase resistance genes can be either chromosomally or plasmid-mediated and are widely distributed in nature. Chloramphenicol resistance is due to the presence of an intracellular enzyme called chloramphenicol transacetylase. This enzyme acetylates hydroxyl groups on the chloramphenicol structure which causes decreased binding to the 50S ribosome.

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Synthesis of a New Metabolic Pathway

Bacteria can produce a new enzyme that is not inhibited by the antimicrobial.

Trimethoprim-sulfamethoxazole resistance is due to bacteria that produce a new dihydrofolate reductase not inhibited by trimethoprim and a new dihydropteroate synthetase not susceptible to sulfonamides.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing has two purposes. First, susceptibility testing is utilized clinically to predict the likely outcome of treating a patient's infection with a particular antimicrobial agent. Second, it can provide a quantitative measurement of susceptibility which can be used to monitor the emergence and prevalence of antimicrobial resistance. Currently, the two most popular susceptibility testing methods are the broth microdilution test and the disk diffusion test.

Broth Microdilution Test

The broth microdilution method is really the miniaturization and mechanization of one of the earliest methods of antimicrobial susceptibility testing, the tube-dilution method. Two-fold dilutions of antibiotics (e.g., 1 microgram/mL, 2 microgram/mL, 4 microgram/mL etc.) are prepared and added to individual wells in disposable plastic microdilution trays containing a liquid bacterial growth medium. The wells are then inoculated with a bacterial suspension of a standardized cell density. Following incubation for 16 to 20 hours, the trays are examined for evidence of bacterial growth in the form of turbidity. The lowest concentration of antimicrobial which prevents visible growth represents the MIC, or minimum inhibitory concentration.

These trays usually contain 96 wells, which allows 12 antibiotics to be tested in a range of eight two-fold dilutions in a single tray. Usually, pre-prepared microdilution antimicrobial trays or "panels", are purchased by most clinical microbiology laboratories. Buying pre-prepared panels saves on labor, time and reagent costs, but a disadvantage is the inflexibility of the antimicrobial selections available in the commercially prepared panels. It is also possible to automate the reading of the trays using photometer/tray readers.

The results are interpreted using the "interpretive criteria" published by the National Committee on Clinical Laboratory Standards (NCCLS). The NCCLS MIC interpretive criteria are established by careful analyses of the pharmacokinetics of a particular drug, microbiological testing, and clinical study results obtained during the the FDA pre-approval phase of commercial antimicrobial development (Jorgenson et al., 1998). "Breakpoint" MICs are established for each antimicrobial and bacterial species combination to categorize an organism as susceptible, intermediate or resistant. The MICs used for veterinary isolates are usually based on human breakpoints of clinical significance, which may lead to difficulty in interpretation of results. In general, although other factors must also be considered in the decision process, it is best to treat an infection due to a specific isolate with one of the antimicrobials having the lowest MIC for that isolate.

Disk Diffusion Test

The disk diffusion test is also known as the Kirby-Bauer procedure. A standardized inoculum is applied onto the entire surface of an agar medium in a large Petri plate. Uniform paper discs, each impregnated with a different antibiotic, or the same antibiotic in varying concentrations, are placed on the surface of the agar. The plates are then incubated for 16 to 18 hours. The antibiotic agent diffuses from the paper disk into the agar, thereby preventing the growth of the organism in a zone around the disc. The width of the zone is measured in millimeters and gives an indication of the sensitivity of the organism to the agent or agents being tested (Frobisher et al., 1974).

The results are interpreted by comparing the zone diameter with the interpretive criteria published by NCCLS. The interpretive criteria for the disk diffusion test categorizes the result as susceptible, intermediate or resistant. Therefore, a qualitative result is usually determined instead of a quantitative MIC. It is possible, however, to calculate an approximate MIC because the zone diameter correlates inversely with the approximate MIC for that antibiotic. The approximate MIC can be calculated with a computer software system which compares the zone-diameter values with standard curves for a species and drug using a linear regression formula (Jorgensen et al., 1998).

Sources of Error

An important source of error in susceptibility testing is that for certain bacterial species, differing qualities of bacterial growth may be due to the growth medium. A resistant organism may be misclassified as susceptible simply because it does not grow well in a particular culture medium. Another source of error is the amount of the inoculum. The ideal inoculum is related to both bacterial species and the specific antimicrobial. In some cases a heavy inoculum is appropriate, a light inoculum is appropriate in others (Phillips, 1998). For example, light inocula are needed for susceptibility tests using sulphonamides and trimethoprim.

Advantages and Disadvantages of Both Methods

The advantages of the disk diffusion procedure are cost effectiveness and flexibility. It is the least expensive method and is very flexible because the selection of the antibiotic discs is done by the user. The disadvantages include the lack of a quantitative result (MIC), and the lack of an automated procedure. Though the qualitative result (susceptible, intermediate, resistant) of this method is thought to be easily interpreted by clinicians, a quantitative result is becoming increasingly important in order to monitor small shifts in susceptibility at the population level. Resistance often develops in degrees, for example, as additional resistance genes or factors are acquired by a specific strain. The MIC is a more precise measurement which can better reflect subtle changes in susceptibility, compared to the categorical result reported for the disk diffusion method (Phillips, 1998). Therefore, the current trend is toward the use of the broth microdilution method, especially the automated instrument methods (Jorgensen et al., 1998).

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Antibiotic Use in U.S. Livestock Production

Antibiotic Use in U.S. Livestock Production

Summary

Antibiotics are used in livestock production as therapeutics, prophylactics, and growth promoters. These drugs assist in sustaining livestock production and in controlling animal infections that may be transferred to humans. The scientific community is concerned increasingly about the transfer of antibiotic resistance and/or antibiotic resistance determinants from animals to humans. These concerns may lead to increased restrictions on the use of antibiotics in animal agriculture and decreased exports. This report lists many of the antibiotics approved for use in livestock production in the United States (U.S.), the European Union (EU), and the United Kingdom (UK). The report also describes the purposes and prevalence of antibiotic use in the U.S. livestock population, based on several different studies by the National Animal Health Monitoring System (NAHMS) between 1990 and 1997. Antibiotics were used in most phases of swine production and were administered via injection, feed, water and orally. The trend was for antibiotic use to increase in swine production between 1990 and 1995. Approximately 25% of small feedlot cattle operations and 70% of large feedlot operations used antibiotics in the feed. Similarly, approximately 31% of cattle on small feedlot operations and 57% of cattle on large feedlot operations received antibiotics via feed. Tetracycline and derivatives of tetracycline were some of the most frequently used in-feed antibiotics on feedlot operations. Varying percentages of dairy operations and varying percentages of dairy cows on these operations were exposed to antibiotics during lactation and the dry period. Only a few antibiotics have been approved for use in catfish production. Romet was used to manage enteric septicemia of catfish on 41% of affected operations. Although specific volumes of antibiotics and the prevalence of antibiotic use in individual animals was not a goal of these studies, increased restrictions on the use of antibiotics could have significant implications for animal health. Developing economically feasible, chemotherapeutic, and non-chemotherapeutic alternatives to antibiotics (e.g., management strategies) may become vital in order to maintain the health of U.S. livestock and to maintain viable export markets.

General Uses of Antibiotics in Livestock Production

Antibiotics are used for three main purposes in livestock production: (1) as therapeutics for managing clinically apparent diseases, (2) as prophylactics at subtherapeutic concentrations (i.e., usually less than 200 grams per ton), and (3) as growth promoters.

Therapeutics

Therapeutic uses of antibiotics are required to manage clinically apparent diseases, and the therapeutic regimen is dictated by label instructions from the manufacturer, or in accordance with extra-label instructions. As in human medicine, antibiotics were used extensively and unnecessarily in veterinary medicine during their early development in the 1950's and through the 1960's (Frost, 1991). Extensive use of the new "wonder drugs" led to diminished emphases on husbandry and hygiene practices that had been used successfully to combat infectious diseases in

livestock populations. The use of therapeutic and prophylactic antibiotics gradually became a part of a balanced, integrated approach to the control of infectious diseases in all species of animals.

Prophylactic, Sub-therapeutic and Growth Promotion

The earliest evidence of the growth-promoting effects of antibiotics became apparent when it was shown that chickens exposed to small doses of chlortetracycline grew more rapidly than nonexposed chickens (Stokstad, 1950). Oral antibiotics, especially those that act on Gram positive organisms, became widely used at sub-therapeutic levels for their consistent ability to improve the growth of livestock (Crawford, 1983; Droumev, 1983). While part of the reason for this practice is to reduce the risk of disease, it is also accepted that regular intake of oral antibiotics as feed additives has a direct nutrient sparing effect and reduces the production of urea, methane, and ammonia in the intestine, among other effects (Vissek, 1978; Walton, 1983). The rationale for the use of antibiotics as growth promoters has been established (Luetzow, 1997). A modulating effect on either the metabolic activity of certain intestinal micro-organisms, or a shift of the balance of the microbial ecosystem, which constitutes an essential part of mammalian digestion, is the proposed mechanism of action. These effects are observed at use levels which are far lower than those achieved in therapeutic use. More efficient digestion during the administration of low levels of anti-microbials decreases the amount of feed necessary to raise and to fatten domestic animals. The beneficial effects of sub-therapeutic doses of antibiotics has not decreased since these effects became known in the 1950's (Frost, 1991).

Besides the claim of growth promotion, secondary effects on the health status at sub-therapeutic levels are also considered by some regulatory agencies (Luetzow, 1997). Direct beneficial effects of the use of oral antibiotics in medicated premixes for livestock include the prevention and relief of suffering caused by pathogenic bacteria. Specific examples in the swine industry include swine dysentery, enterotoxigenic *Escherichia coli*, and porcine proliferative enteropathy, but similar examples exist in other livestock husbandry systems (McOrist, 1997).

Antibiotics used in Livestock Production in U.S.

Table 1. Antibiotics and sulfonamides approved by the U.S. FDA for use in dairy and beef cattle. These antibiotics and sulfonamides may be used for growth promotion and feed efficiency, therapeutic purposes, or both (U.S. Food and Drug Administration, 1998).

Amoxicillin	Lacalocid	Tylosin
Ampicillin	Monensin	Sulfabromomethazine
Bacitracin	Neomycin	Sulfachloropyridazine
Ceftiofur	Oxytetracycline (oral)	Sulfadimethoxine
Chlortetracycline	Oxytetracycline (injection)	Sulfaethoxyypyridazine
Dihydrostreptomycin	Penicillin	Sulfamethazine
Erythromycin	Streptomycin	Sulfamethoxine
Furamazone	Tetracycline	
Gentamycin	Tilmicosin	

Table 2. Antibiotics approved by the U.S. FDA for use in hogs. These antibiotics may be used for growth promotion and feed efficiency, therapeutic purposes, or both (U.S. Food and Drug Administration, 1998).

Amoxicillin	Efrotomycin	Penicillin
Ampicillin	Erythromycin	Spectinomycin
Apramycin	Gentamycin	Streptomycin
Arsanilic acid	Lincomycin	Tetracycline
Bacitracin	Neomycin	Tiamulin
Bambermycins	Oleandomycin	Tylosin
Chlortetracycline	Oxytetracycline	Virginiamycin

Table 3. Chemotherapeutics and sulfonamides approved by the U.S. FDA for use in hogs. These chemotherapeutics and sulfonamides may be used for growth promotion and feed efficiency, therapeutic purposes, or both (U.S. Food and Drug Administration, 1998).

Arsanilate sodium	Roxarsone	Sulfamethazine
Arsanilic acid	Sulfaethoxypyridazine	Sulfathiazone
Carbadox	Sulfachlorpyridazine	

Table 4. Antibiotics approved by the U.S. FDA for use in sheep. These antibiotics may be used for growth promotion and feed efficiency, therapeutic purposes, or both (U.S. Food and Drug Administration, 1998).

Chlorotetracycline	Neomycin	Penicillin
Erythromycin	Oxytetracycline	Penicillin/streptomycin

Table 5. Antibiotics approved by the U.S. FDA for use in chickens and turkeys. These antibiotics may be used for growth promotion and feed efficiency, therapeutic purposes, or both (U.S. Food and Drug Administration, 1998).

Bambermycin	Novobiocin	Streptomycin
Bacitracin	Oleandomycin	Tetracycline
Chlortetracycline	Oxytetracycline	Tylosin
Erythromycin	Penicillin	Virginiamycin
Gentamycin	Roxarsone	Fluoroquinolones
Neomycin	Spectinomycin	

Table 6. Coccidiostats approved by the U.S. FDA for use in broilers, turkeys, and layers. Not every coccidiostat in the three categories in the table has been approved for use in all three of these areas of production (U.S. Food and Drug Administration, 1998).

Ionophores	Sulfonamides	Others
Lasalocid	Sulfachloropyrazine	Amprolium

Maduramycin	Sulfamethazine	Arsanilate
Monensin	Sulfadimethoxine	Buquinolate
Narasin	Sulfamyxin	Clopindol
Salinomycin	Sulfanitran	Dequinat
	Sulfaquinoxaline	Nequinat
		Nicarbazin
		Robenidine
		Zoalene

Table 7. Therapeutic antimicrobial and sulfonamides authorized in the United Kingdom (adapted from Rutter, 1997).

Amoxycillin	Cloxacillin	Spectinomycin
Ampicillin	Danofloxacin mesylate	Spiramycin
Apramycin	Dihydrostreptomycin	Streptomycin sulphate
Baquiloprim	Enrofloxacin	Sulphachlorpyridazine
Benzathine penicillin	Erythromycin	Sulphadiazine
Benzyl Penicillin	Florfenicol	Sulphadimidine
Cefquinome	Framycetin sulphate	Sulphadoxine
Ceftiofur	Lincomycin	Sulphamethoxypyridazine
Cephalexin	Marbofloxacin	Sulphaquinoxalone
Cefoperazone	Nafcillin	Sulphatrazoxole
Cefuroxime	Neomycin sulphate	Tetracycline hydrochloride
Cephacetrile sodium	Novobiocin	Tiamulin (fumarate)
Cephalonium	Oxolinic acid	Tilmicosin
Chloramphenicol	Oxytetracycline	Trimethoprim
Chlortetracycline	Phenoxymethyl penicillin	Tylosin
Clavulanic acid	Procaine penicillin	

Table 8. Antibiotic growth promoters that have been approved, not approved or banned by the European Union (EU). The table compares the legal status of active substances for the compounds currently used at a significant degree. The approval status of any one antibiotic does not refer to the status of the antibiotic as a therapeutic or prophylactic agent (e.g., use as coccidiostat in the European Union) (adapted from Luetzow, 1997).

Antibiotic	Approval Status
Avilamycin	approved
Avoparcin	banned; re-evaluation
Bacitracin Zn	approved
Bambermycin	not approved
Lasalocid	only as coccidiostat
Lincomycin	not approved
Monensin	approved
Salinomycin	approved

Spiramycin	approved
Tylosin	approved
Virginiamycin	approved

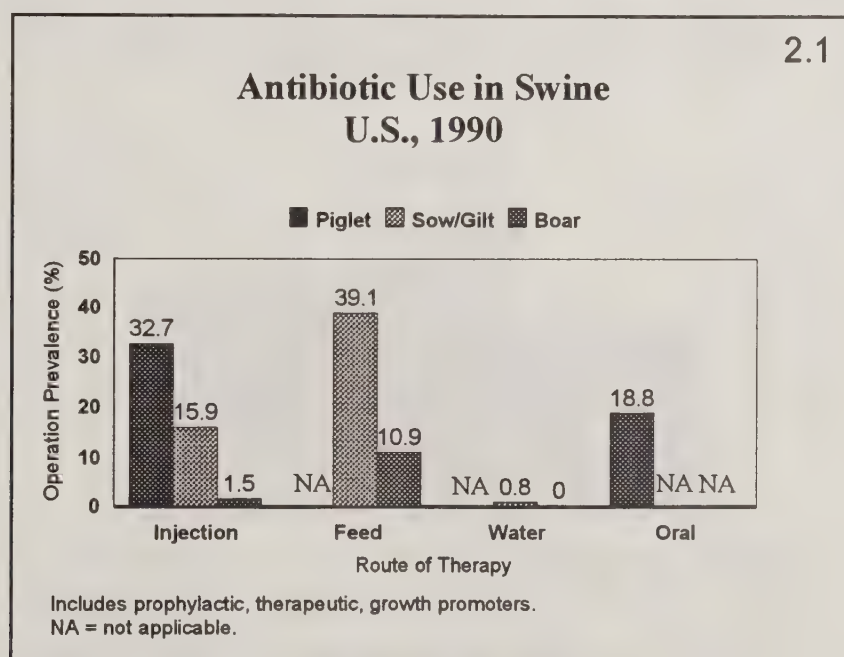
Table 9. Antibiotic growth promoters that have been approved by the United Kingdom (adapted from Rutter, 1997).

Avilamycin	Monensin Sodium	Spiramycin
Bacitracin Zinc	Olaquinox	Tylosin Phosphate
Flavophospholipol	Salinomycin Sodium	Virginiamycin

Prevalence of Antibiotic Use on U.S. Livestock and Poultry Operations

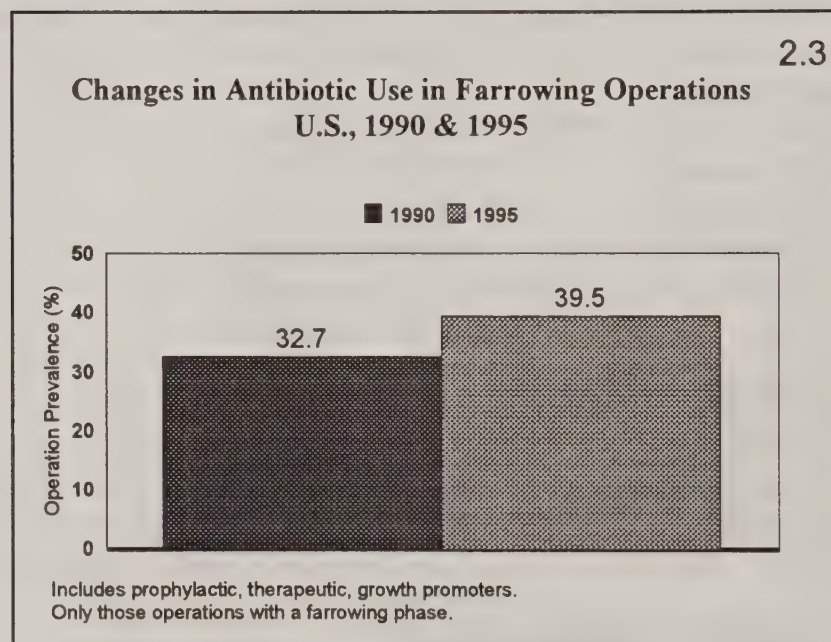
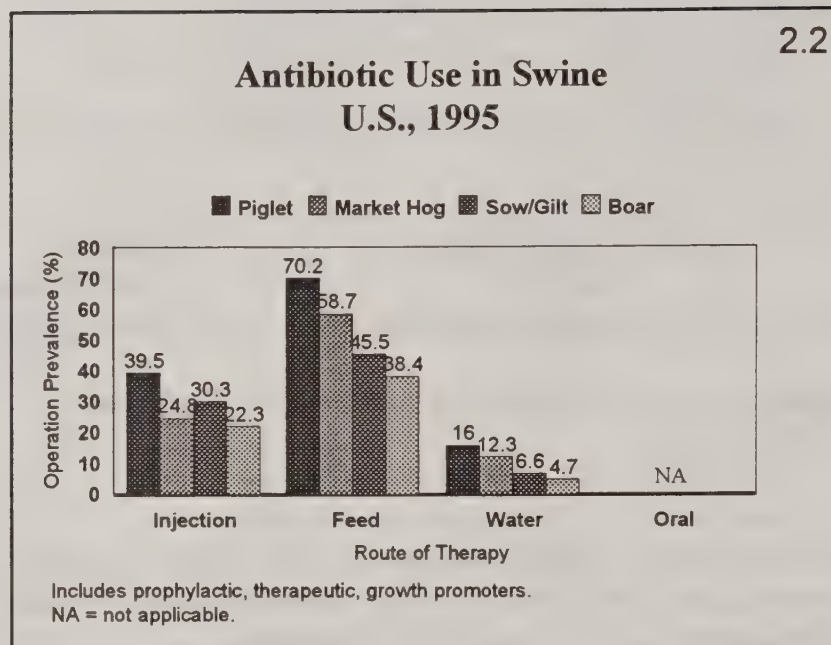
Swine

Antibiotics are approved for use in swine for growth promotion ($n = 5$), therapeutics ($n = 11$), and both growth promotion and therapeutics ($n = 5$) (National Research Council Institute of Medicine 1998, Agrimetrix Associates, Inc., 1994). According to the national population estimates from the NAHMS Swine '90 Study, antibiotics were given to piglets via injection and orally (USDA/APHIS/VS, 1992a) (**Figure 2.1**). Antibiotics were given to females (i.e., sows and



gilts) via injection and in the feed, but rarely in the water (**Figure 2.1**). Boars were rarely given antibiotics, regardless of the route (**Figure 2.1**). In addition to the three production groups (i.e., pigs, females, and boars) that were included in the NAHMS Swine '90 Study, antibiotic use in market hogs was examined in the NAHMS Swine '95 Study (USDA/APHIS/VS, 1995e).

Generally, the prevalence of antibiotic use in market hogs in 1995 was similar to prevalence of antibiotic use in piglets and females, for a specific route of therapy (**Figure 2.2**). Operations with a farrowing phase that used antibiotics via injection increased from 32.7% in 1990 to 39.5% in 1995 (**Figure 2.3**). Antibiotic use via injection and via water increased for piglets, sows and gilts,

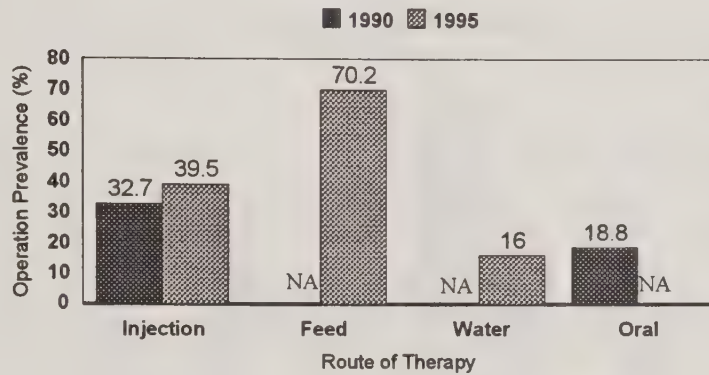


and boars between 1990 and 1995, and use via feed increased dramatically for each group (**Figures 2.4, 2.5, 2.6**). It cannot be determined if there was a similar trend for market hogs, because the baseline data for market hogs was not collected during the NAHMS Swine '90 Study.

Antibiotic use was examined prospectively in cohorts of piglets and females during the NAHMS Swine '90 Study (USDA/APHIS/VS, 1992a). The percentages of piglets that were given antibiotics via injection and orally were 60.4% and 10.4%, respectively (**Figure 2.7**). The percentage of females that were given antibiotics via any route was 30.6%. Females were given antibiotics via injection far more frequently than via other routes (**Figure 2.7**).

Changes in Antibiotic Use in Piglets U.S., 1990 & 1995

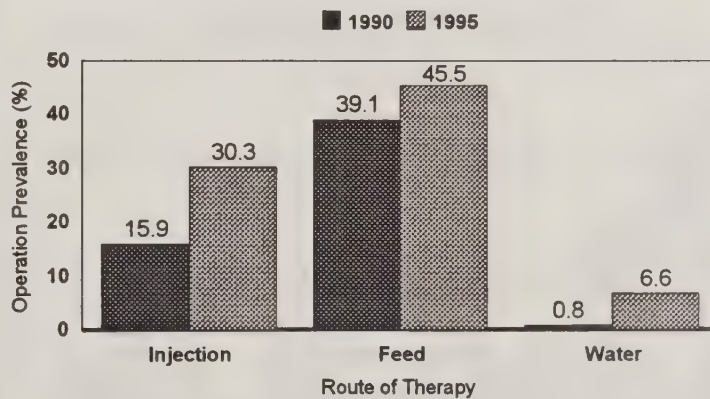
2.4



Includes prophylactic, therapeutic, growth promoters.
NA = not available.

Changes in Antibiotic Use in Sows and Gilts U.S., 1990 & 1995

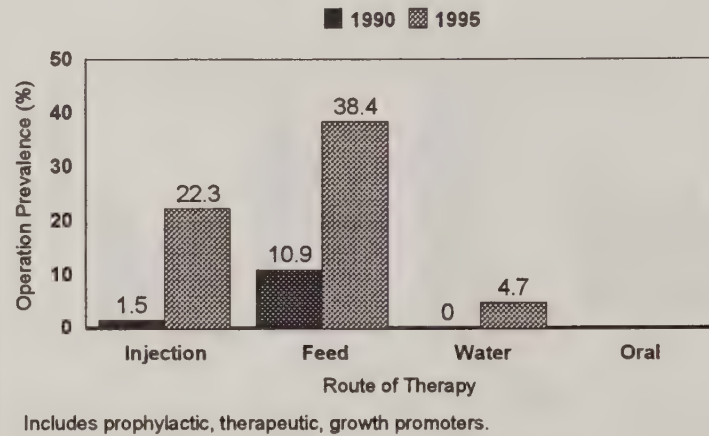
2.5



Includes prophylactic, therapeutic, growth promoters.

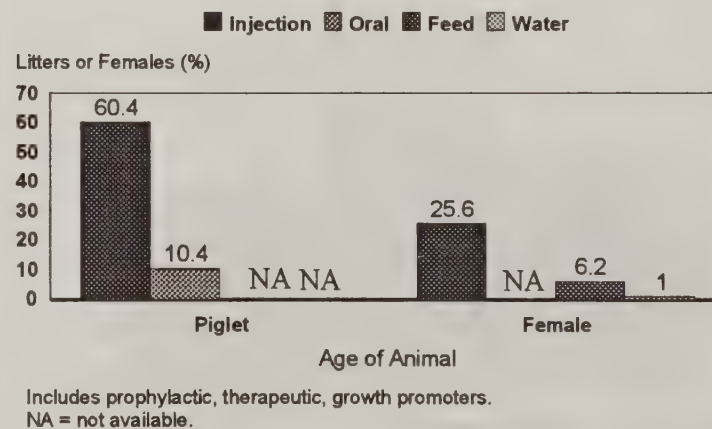
2.6

Changes in Antibiotic Use In Boars U.S., 1990 & 1995



2.7

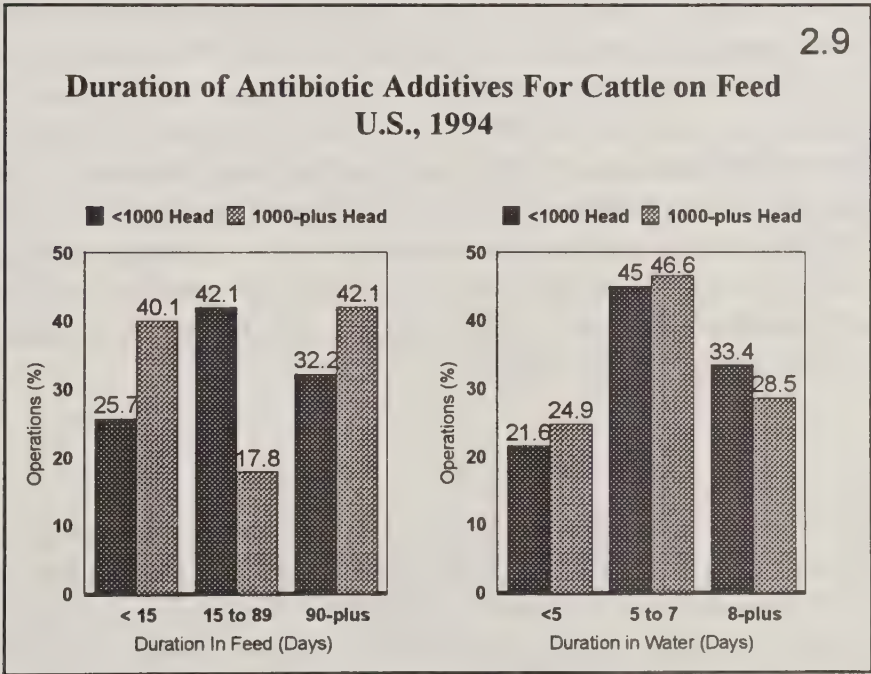
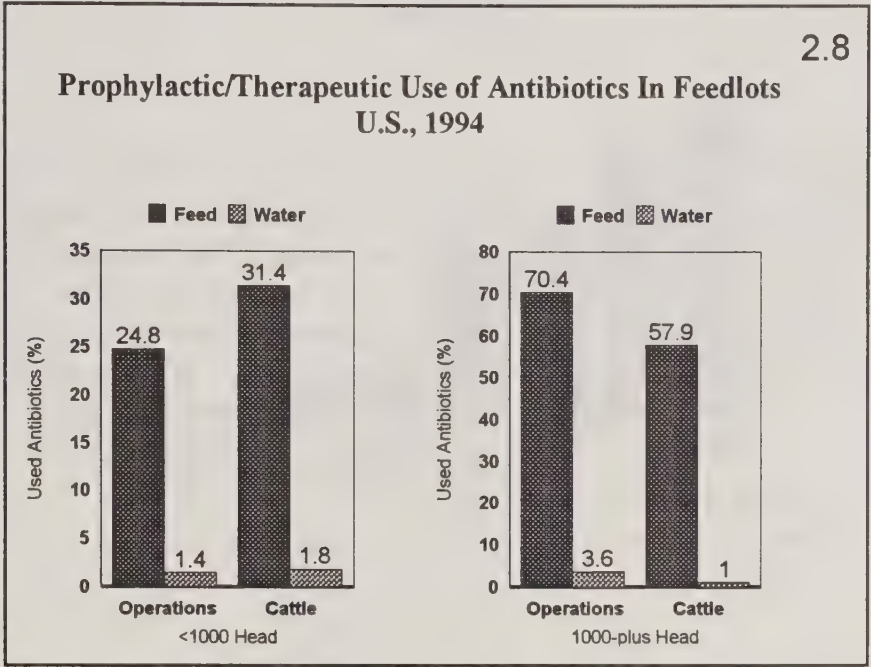
Prospective Antibiotic Use in Piglets and Females U.S., 1990



Cattle-on-Feed

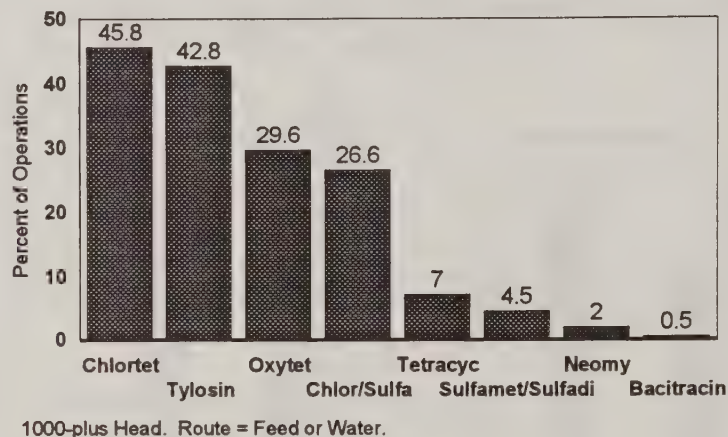
Antibiotics were used in the feed and water on feedlot operations of all sizes in 1994 (USDA/APHIS/VS, 1995b). Large operations, defined as those operations with a capacity of more than 1000 head, were almost three times as likely to use antibiotics in the feed and in the water, when compared to small operations (**Figure 2.8**). The cattle on the large operations were almost twice as likely to receive antibiotics in their feed and water, when compared to cattle on the small operations (**Figure 2.8**). The feedlot cattle were exposed to antibiotics in the feed for

90 days or longer on 42% of the large operations and on 32% of the small operations (Figure 2.9). These cattle were exposed to antibiotics in the water for 8 days or longer on 28% of the large operations and on 33% of the small operations (Figure 2.9). Chlortetracycline and tylosin,



the most frequently used antibiotics in feed or water, were used each by more than 40% of the feedlot operations (Figure 2.10).

Antibiotic Additives For Cattle-On-Feed U.S., 1994



Dairy

Dairy '96 studied antibiotic use in dairy cows during the 12 months prior to interviewing the producers (USDA/APHIS/VS, 1996d). Antibiotics were given by injection to 1 to 9% of the milk cows on 48.9% of the operations, and they were given to 10 to 39% of the milk cows on 39.5% of the operations. Only 3.9% of the operations gave no antibiotics via injection. Antibiotics were given by injection during lactation to 1 to 39% of the milk cows on 87.8% of the operations. Only 6.5% of the operations gave no antibiotics via injection during lactation. Antibiotics were given by injection during the dry period to 1 to 39% of the milk cows on 47.3% of the operations. Slightly more than 50% of the operations gave no antibiotics via injection during the dry period. Additional details about routes of injection, sites of injection, the veterinarian's role, antibiotic record systems, and identification of animals having undergone therapy are available from Dairy '96, but have not been presented in this report.

Poultry

Poultry became the focus of a national study by the NAHMS program for the first time in early 1999. Thus, unlike the swine, beef, dairy and the catfish industries, there are no data from the NAHMS program on antibiotic use in the poultry industry. However, a summary of the cost of antibiotic used in broiler and turkey production in the U.S. from 1989 through 1994 has been compiled (Agrimetrix Associates, Inc., 1994). Antimicrobial drugs used were categorized as sulfonamides (n = 6), ionophores (n = 5), miscellaneous (e.g., amprolium; n = 9), antibiotics for growth promotion only (n = 1), antibiotics for infectious diseases only (n = 8), and antibiotics for both growth promotion and infectious diseases (n = 8). These antimicrobials are given to poultry in feed, water, and less frequently via injection. The poultry industry is concerned that only one antibiotic, a fluoroquinolone, has been approved in recent years as a therapeutic for poultry. On

the other hand, the amount of antibiotics used in broiler production between 1989 and 1994 decreased for several reasons, among these being the implementation of multi-faceted preventive medicine programs (e.g. biosecurity), increased efforts to reduce production costs, enhanced focus on residue avoidance, and rapid production of efficacious vaccines by manufacturers.

Catfish

Catfish '97 was the first national study of food fish by the NAHMS program (USDA/APHIS VS, 1997b). Enteric Septicemia of Catfish (ESC), a bacterial infectious disease, was reported by 56% of U.S. operations. Antimicrobial drug use was not a specific focus of Catfish '97, because very few antibiotics have been approved for use in catfish production, and even fewer antibiotics are thought to be efficacious (Personal communication, Bruce Wagner, USDA/APHIS VS, 1999). However, ESC was managed by 41% of these affected operations by feeding Romet, a combination of sulfadimethoxine and ormetoprim.

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**Prevalence of *Salmonella spp.* and *Escherichia coli*
on U.S. Livestock Operations**

Prevalence of *Salmonella* spp. and *Escherichia coli* On U.S. Livestock Operations

Summary

Salmonella and *Escherichia coli* (*E. coli*) are associated with significant morbidity and mortality in livestock and therefore are two of the most economically significant pathogens of livestock. In humans, *Salmonella* and *E. coli* are important causes of food-borne illness. The Centers for Disease Control and Prevention (CDC) estimates 1.4 million *Salmonella* cases with 600 deaths occur each year. Morbidity and mortality from *Salmonella* leads to significant economic losses to the population through medical expenses and decreased productivity. Since antimicrobial drugs are used in livestock to control these two pathogens, there is concern about antibiotic resistance development in these pathogens and subsequent transfer of that resistance to humans through contaminated food. The prevalence of these two pathogens in livestock therefore may impact the level of antibiotic use, antibiotic resistance development and human food-borne disease. This concern provides impetus for thoroughly understanding the ecology and epidemiology of *Salmonella* and *E. coli* infections in animals.

The objective of this report is to provide an abbreviated review of *Salmonella* and *E. coli* infections, and present the descriptive results of several national studies by the USDA's National Animal Health Monitoring System (NAHMS) of *Salmonella* and *E. coli* on U.S. livestock operations. *Salmonella* were found in animals on dairy, feedlot, and swine operations. None of the *Salmonella* serotypes from feedlot cattle were among the CDC's list of the top 5 *Salmonella* isolates from humans in 1991. However, three of the serotypes from swine were among the CDC's list of the top 5 *Salmonella* isolates from humans in 1994. *E. coli* O157:H7 was detected in dairy calves and feedlot cattle, but the prevalence generally was low in comparison to the prevalence of some other pathogens. Diseases in swine that may be caused by *E. coli* were reported to be an important cause of morbidity and mortality on swine operations.

Salmonella

Salmonellosis is a ubiquitous disease caused by members of the genus *Salmonella* (Nietfeld et al., 1999). There are more than 2300 serotypes of *Salmonella*. Clinically, salmonellosis in pigs may be systemic, enteric, or inapparent, and may be acute or chronic. *Salmonella choleraesuis* is associated with acute septicemia and enterocolitis, and it accounts for 70% to 90% of all serotypes isolated from clinically ill pigs. *Salmonella typhimurium*, the second most common serotype of pigs, causes acute enterocolitis. *S. dublin*, *S. typhimurium*, *S. newport*, *S. montevideo*, and *S. anatum* are important serotypes of dairy and beef cattle. *S. dublin*, once confined to cattle in the Pacific northwest in the U.S., is becoming more widespread geographically. Salmonellosis in lambs is most prevalent in feeders. *S. abortus ovis* is associated with abortion in ewes. Salmonellosis in goats is reported to be similar to salmonellosis in cattle.

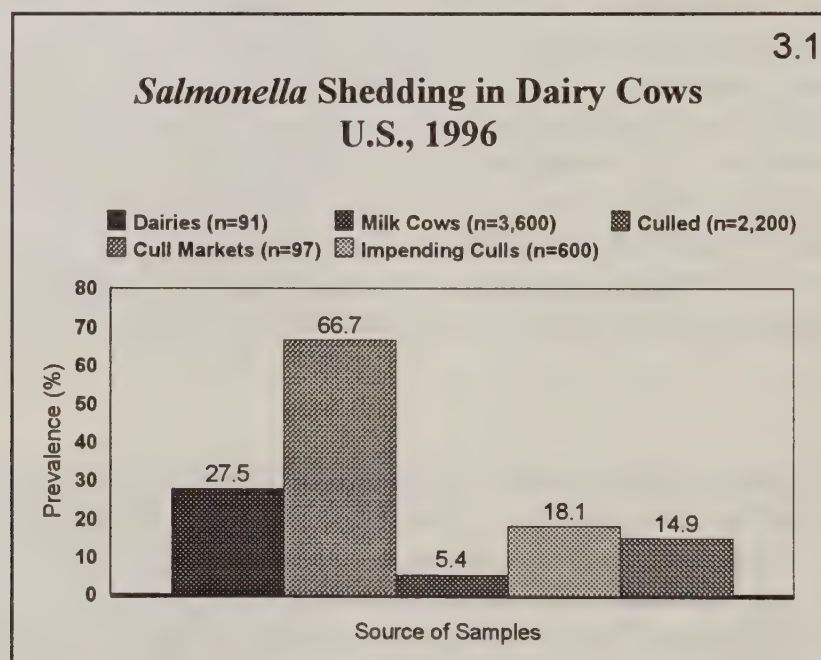
Salmonella spp. are some of the most common food-borne pathogens of humans (Roberts, 1988; Bean, 1990). The estimated costs of food-borne illness of bacterial origin in the U.S. is \$2.9 to 6.7 billion annually (Buzby, 1995; Buzby, 1996). Estimated costs associated with human salmonellosis are nearly one billion dollars annually (range 0.6 to 3.5 billion). Beef, dairy, pork,

poultry, and seafood are documented vehicles for transmission of *Salmonella* from animals to humans during these outbreaks (Bean, 1990). Thus, animals that shed *Salmonella* may become a source of human infections. Of no less concern, is the potential transfer of antimicrobial resistant *Salmonella* spp. or their resistance determinants from animals to humans (World Health Organization, 1997). Accordingly, several national epidemiologic studies of *Salmonella* in U.S. livestock populations were undertaken to provide a scientific basis for addressing relationships between the infections in humans and animals.

Descriptive Epidemiology of *Salmonella* in the U.S.

Dairy Cows

A survey of *Salmonella* was included in the NAHMS Dairy '96 Study (USDA/APHIS/VS, 1998). Fecal samples were collected from a total of 4,200 cows, 3,600 milk cows and 600 impending cull cows (i.e., 7 days prior to culling), on 91 dairy operations in 19 states. Samples also were collected from 2,000 dairy cows from 97 cull-cow markets. The operation prevalence of fecal shedding of *Salmonella* on dairy operations and in cull-cow markets was 27.5% and 66.7%, respectively (Figure 3.1). The individual-cow prevalence in milk cows and cull cows



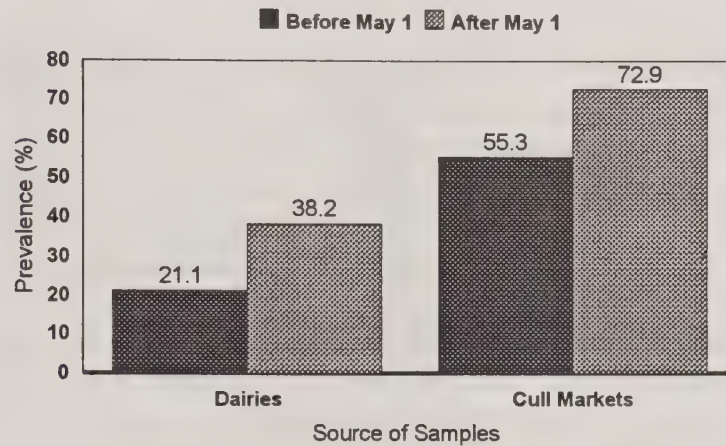
from these operations and markets was only 5.4% and 14.9%, respectively. The operation prevalence of shedding was higher during the three-month period after May 1, 1996 versus the three-month period before May 1 (Figure 3.2). Similarly, the individual-cow prevalence of shedding was higher during the three-month period after May 1, 1996 versus the three-month period before May 1 (Figure 3.3).

Dairy Calves

A national study of the prevalence of *Salmonella* in U.S. dairy calves was done in 1991-1992 (USDA/APHIS/VS, 1994). Dairy producers from 28 states were selected to represent herds of

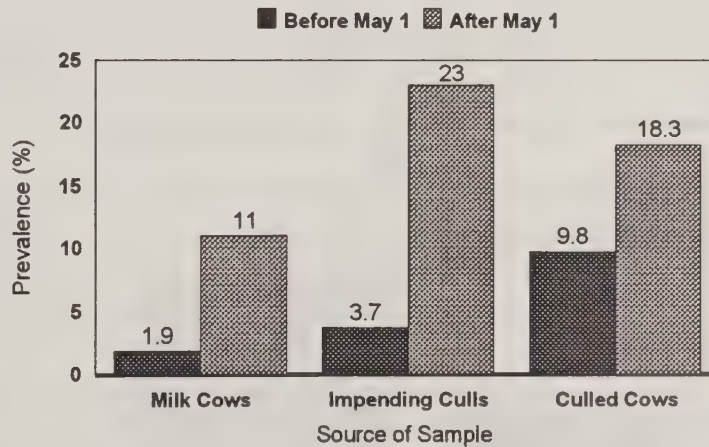
3.2

Seasonal Shedding of *Salmonella* in Dairy Cows U.S., 1996



3.3

Seasonal Shedding of *Salmonella* In Dairy Cows U.S., 1996

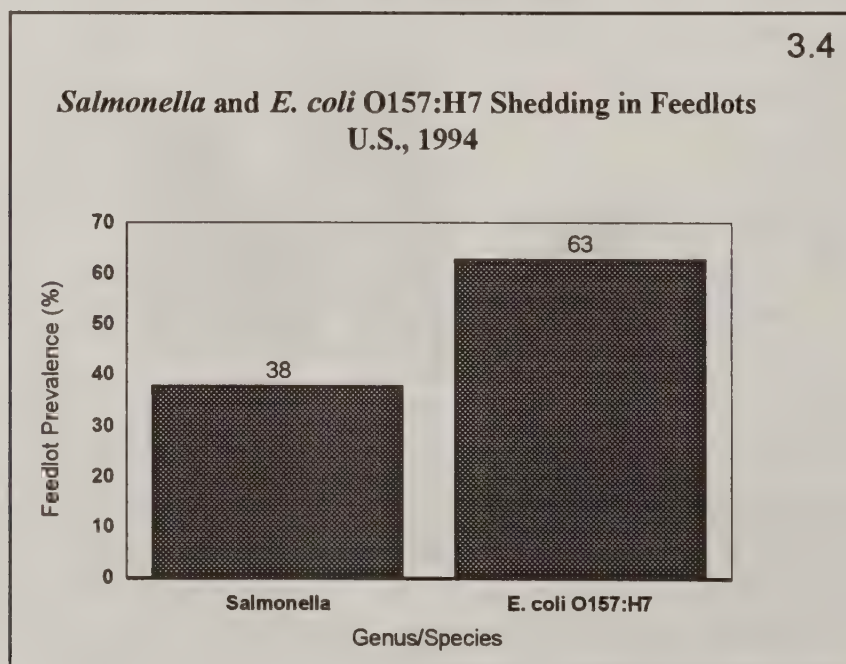


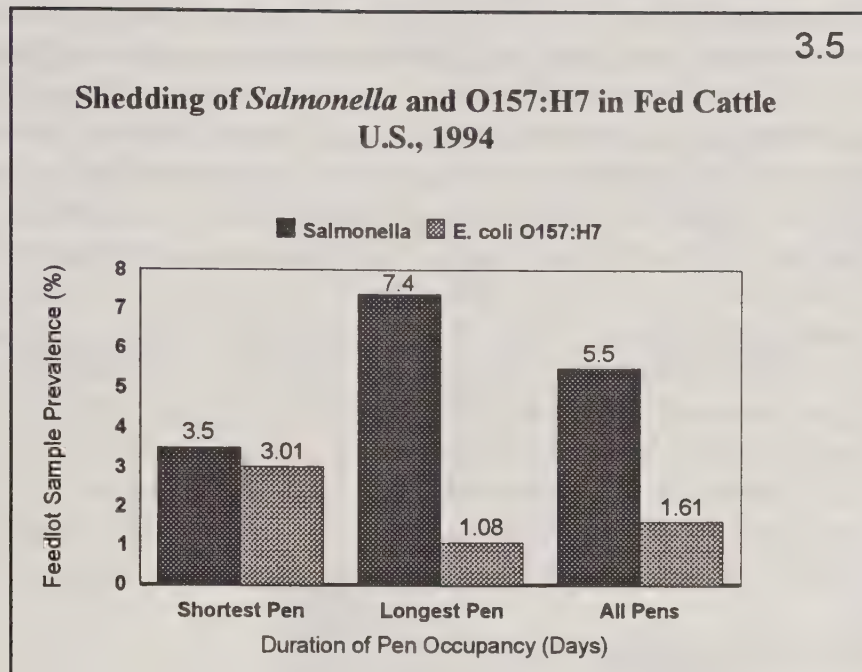
30 or more cows and also represent 78% of the National dairy cow population. Producers were given the option of having fecal specimens evaluated for *Salmonella*. The prevalence of *Salmonella* in specimens from 6,862 calves was 2.1%. The most prevalent serotype was *S. typhimurium*, which comprised 27.6% of 145 positive samples. *S. dublin* comprised 10.3% of the positive samples. Other serotypes were *S. mbandaka*, *S. muenster*, *S. anatum*, *S.*

cerro, and *S. typhi copenhagen*. The geographic distribution of the infection was widespread, but the region-specific prevalence was highest in the south, where 34.1 were positive per 1,000 specimens tested. The prevalence was lowest in the northeast region, 15.0 per 1,000 specimens. The prevalence was highest in herds of 100-plus cows (25.0 positives per 1,000 specimens) and lowest in herds of 51 to 100 cows (11.9 positives per 1,000 specimens).

Feedlot Cattle

During the NAHMS 1994 Cattle on Feed Evaluation (COFE), a stratified random sample of feedlot operations from the 13 leading cattle-feeder states was selected for COFE (USDA/APHIS/VS, 1995). The number of operations that responded was 498, and 100 of the 498 operations with a capacity of at least 1,000 cattle volunteered to have samples collected from their feedlots. In each feedlot, 25 samples were collected from fresh feces on the floor of two pens, one pen having the shortest duration of occupancy, and the other pen having the longest duration of occupancy. A total of 4,977 samples from 200 pens on the 100 operations were tested for *Salmonella* at the National Animal Disease Center. The operation prevalence was 38.0%, and the sample prevalence was 5.5% (**Figures 3.4 and 3.5**). Shedding of *Salmonella* was more prevalent in southern feedlots. *Salmonella* was more prevalent on operations and in pens that were classified as having a “long-duration of occupancy” by the cattle versus those that were classified as having a “short-duration of occupancy” by the cattle (**Figure 3.5**). A single serotype was found on 42.1% of the 38 positive operations, and multiple serotypes were found on the remaining 57.8% of the positive operations. The five most common serotypes were *S. anatum*, *S. montivideo*, *S. muenster*, *S. kentucky*, and *S. newington*. Unlike swine (refer to discussion below), none of the serotypes from the 1994 COFE were among the CDC’s list of the top 5 *Salmonella* isolates from humans in 1991.





Swine

During the NAHMS Swine '95 Study, 160 swine operations were selected to participate in a survey of *Salmonella* in finisher hogs (USDA/APHIS/VS, 1997). The NAHMS Swine '95 study included pork operations in 16 states that contained 91% of the U.S. hog inventory. A total of 6,655 samples that were collected from 988 pens on 152 operations were tested for *Salmonella* at the National Animal Disease Center. A "positive", regardless of whether reference is being made to an operation or a pen, was defined as one with at least one positive sample, and these "positives" were used to determine the operation prevalence, pen prevalence and sample prevalence.

The operation prevalence of *Salmonella* was 38.2%. The prevalence varied among 3 distinct geographic regions from 29.9% to 65.5%. The trend of increasing herd size continues in the swine industry, and unfortunately, *Salmonella* shedding was more prevalent on large operations. The pen prevalence of *Salmonella* in the 998 pens was 17.5%. Of the 10 pens sampled per farm, the prevalence was from 10% to 100%. The sample prevalence in the 6,655 samples was 6.0%. The 10 most frequent serotypes that are shed by finisher hogs accounted for 85.0% of the isolates from Swine '95. A single serotype was found on 60.3% of the positive operations, and multiple serotypes were found on the remaining 39.7% of the positive operations. Four of the serotypes are on the CDC's list of the top 10 *Salmonella* isolates from humans. Carcass contamination as a possible source of these human isolates is a concern of the CDC, regardless of whether the isolates are susceptible or resistant to antibiotics.

Escherichia coli

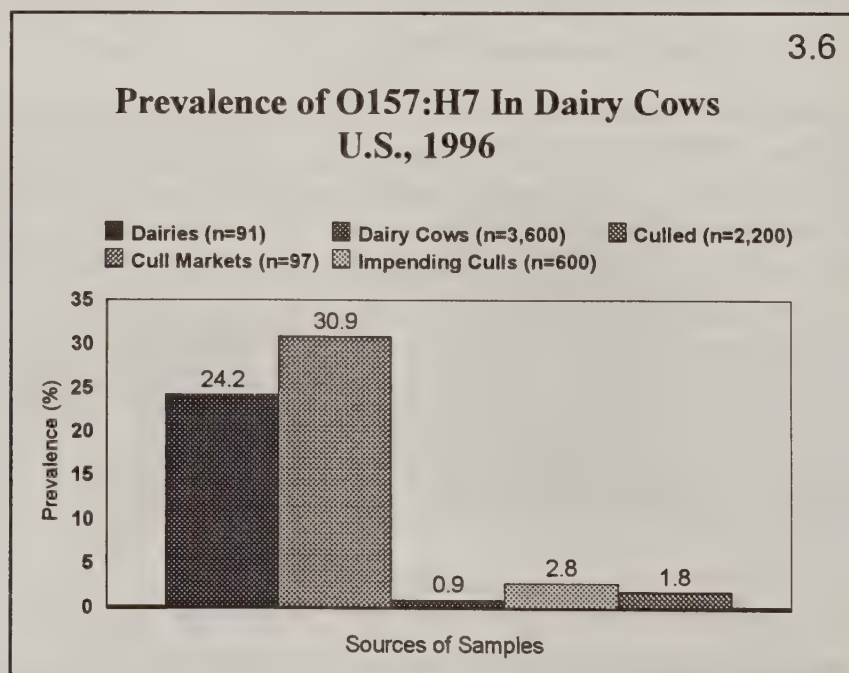
Most mammalian species are susceptible to *Escherichia coli* infections (Fairbrother, 1999). The most frequent clinical manifestations of *E. coli* infection are neonatal and postweaning diarrhea

(i.e., scours) and edema disease in young pigs, dysentery, septicemia in young calves and lambs, and mastitis in adult cattle (Fairbrother, 1999). The most important pathotypes in livestock are enterotoxigenic, verotoxigenic, attaching and effacing, septicemic, and nonsepticemic extraintestinal *E. coli*. Strains of a restricted number of subgroups are pathogenic. These strains are classified into pathotypes, based on the production of virulence factors. For example, the enterotoxigenic *E. coli* (ETEC) pathotype is associated with diarrhea in farm animals, and the enterohemorrhagic *E. coli* (EHEC) pathotype is associated with bloody diarrhea in humans. *E. coli* are classified into 150 to 200 serogroups. The predominant serogroup of EHEC that is associated with human disease is O157:H7. Interest in *E. coli* O157:H7 has grown since the large human outbreak in the western U.S. in 1993. Food items such as ground beef, dry fermented sausage, unpasteurized milk, and apple juice, and also nonchlorinated water and recreational water, are vehicles for transmission of O157:H7 (USDA/APHIS/VS, May 1997). Antibiotic resistance genes also have been traced from *E. coli* in animals to *E. coli* in humans (World Health Organization, 1997). Several national epidemiologic studies of *E. coli* in U.S. livestock populations were undertaken, as they were undertaken with *Salmonella*, to provide a scientific basis for exploring the relationships between the infections in animals and humans.

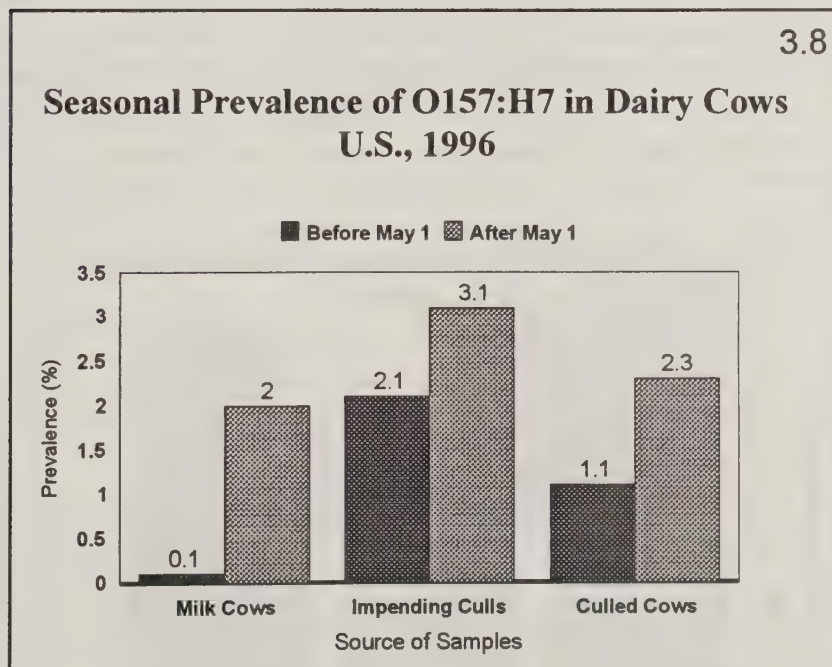
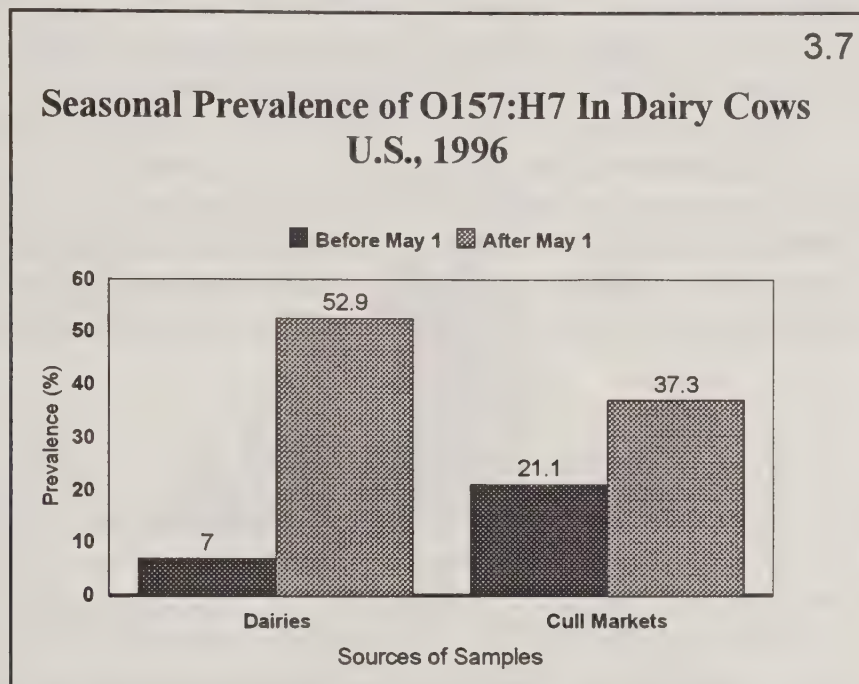
Descriptive Epidemiology *Escherichia coli* O157:H7

Dairy Cows

A survey of *E. coli* O157:H7 also was included in the NAHMS Dairy '96 Study (USDA/APHIS/VS, 1998). Fecal samples were collected from a total of 4,200 cows, 3,600 milk cows and 600 impending cull cows (i.e., 7 days prior to culling), on 91 dairy operations in 19 states. Samples also were collected from 2,000 dairy cows from 97 cull-cow markets. The operation prevalence of fecal shedding of verotoxigenic *E. coli* O157:H7 on dairy operations and in cull-cow markets was 24.2% and 30.9%, respectively (**Figure 3.6**). However, the



individual-cow prevalence in dairy cows and cull cows was only 0.9% and 2.8%, respectively. Regardless of the low prevalence, it has been shown that nearly all dairy operations will be positive for O157:H7, if samples are collected from the operations repeatedly (Hancock et al., 1997). As with *Salmonella*, the operation prevalence of fecal shedding of O157:H7 was higher during the three-month period after May 1, 1996 versus the three-month period prior to May 1 (Figure 3.7), and the individual-cow prevalence of fecal shedding was higher during the three-month period after May 1, 1996 versus the three-month period prior to May 1 (Figure 3.8).



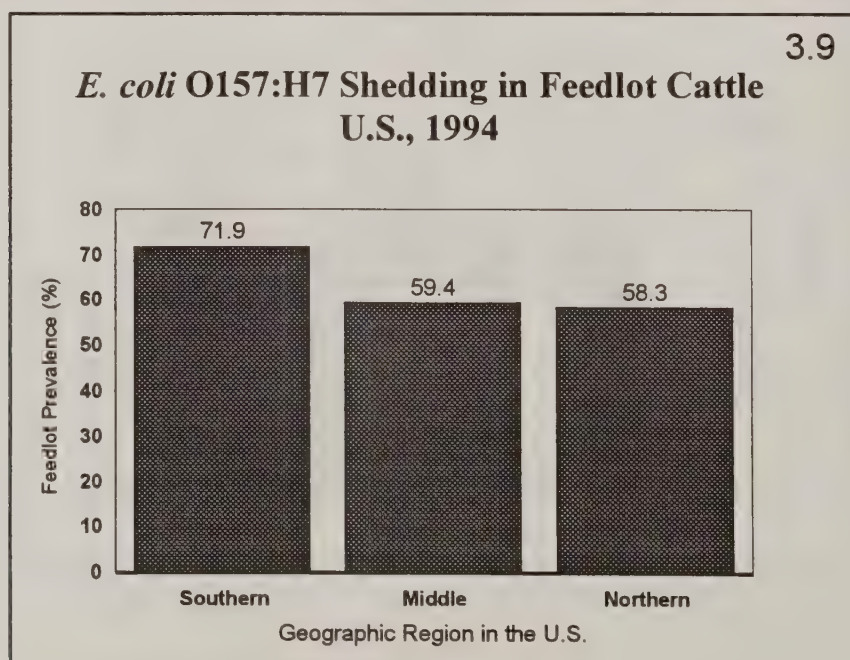
The operation prevalence of fecal shedding of O157:H7 was 39.1% in herds with 100 or more milk cows and 8.9% in smaller herds. Given that the size of dairy herds, like swine herds, is increasing, the potential implications of a higher prevalence of O157:H7 in larger herds should be of concern.

Dairy Calves

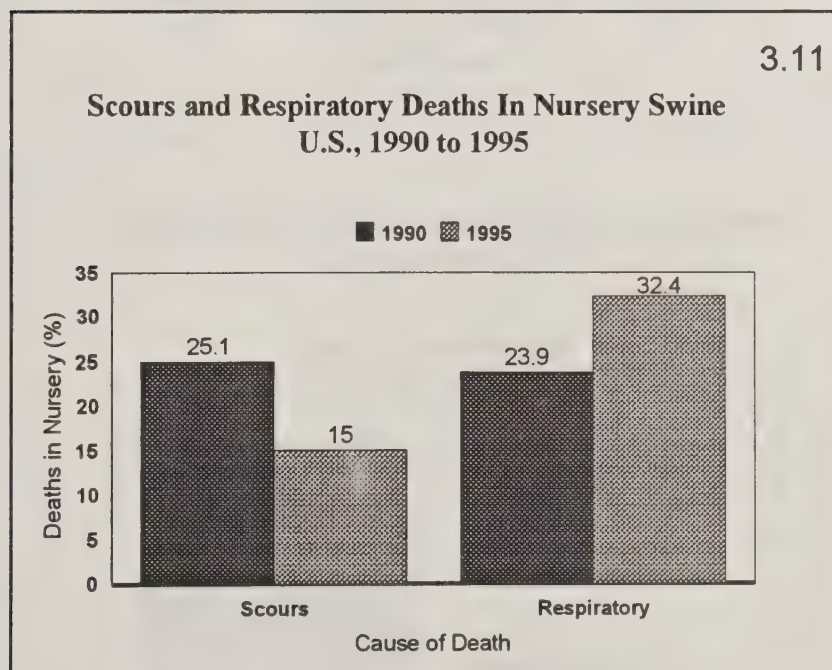
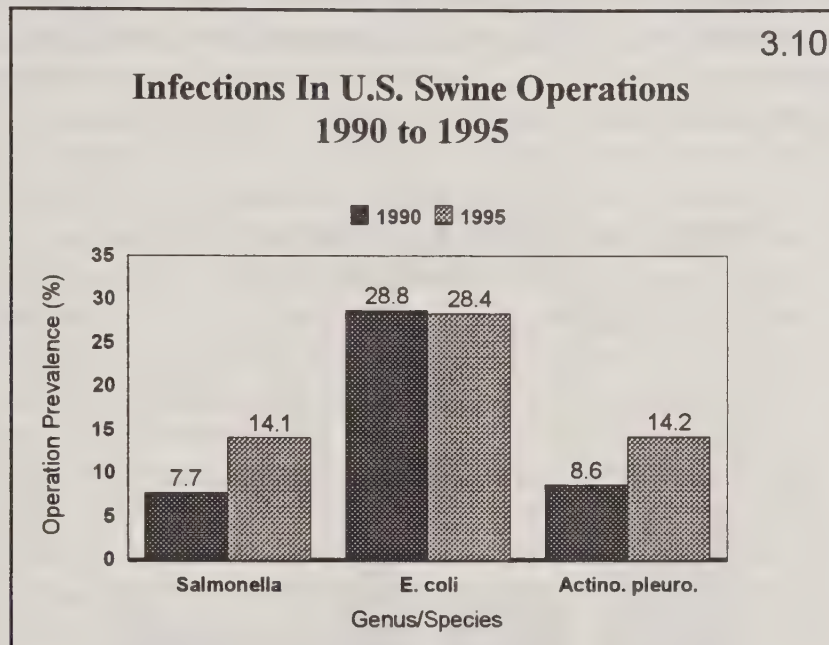
A national study of the prevalence of *Escherichia coli* O157:H7 in U.S. dairy calves was done in 1991-1992 (USDA/APHIS/VS, 1994). The National Dairy Heifer Evaluation Project (NDHEP) included 1,811 dairy operations from 28 states. The operations were selected to represent herds of 30 or more cows and also represent 78.0% of the National dairy cow population. The prevalence of O157:H7 in specimens from approximately 7,000 calves was 3.6%. The geographic distribution of the infection was widespread and rather evenly distributed. A prospective study of 64 of the original herds, 50 of which were negative, showed that the status of the infection for a given herd may change. Infected calves were found on 22.0% of the 50 negative herds, as well as 50% of the herds that were positive originally. The prevalence of infection was higher in weaned calves.

Feedlot Cattle

A survey of O157:H7 also was included in the NAHMS 1994 Cattle on Feed Evaluation (COFE) (USDA/APHIS/VS, 1995). In each feedlot, 30 samples were collected from fresh feces on the floor of two pens, one pen having the shortest duration of cow-occupancy, and the other pen having the longest duration of occupancy. Two additional pens were selected randomly for sampling, if available. A total of 11,881 samples from 400 pens on the 100 operations were tested for O157:H7 at the National Veterinary Services Laboratory and Washington State University. The operation prevalence of O157:H7 was 63.0%, and the sample prevalence was 1.61% (**Figures 3.4 and 3.5**). The operation prevalence was at least 12% higher in the Southern region (**Figure 3.9**). *E. coli* O157:H7 was more prevalent on operations and in pens that were classified as having a “short-duration of occupancy” versus those that were classified as having a



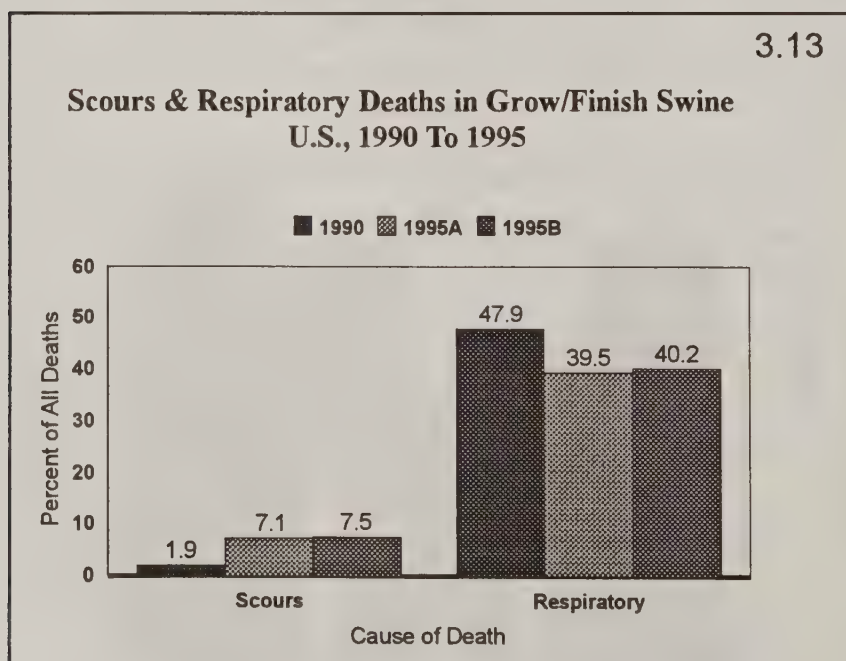
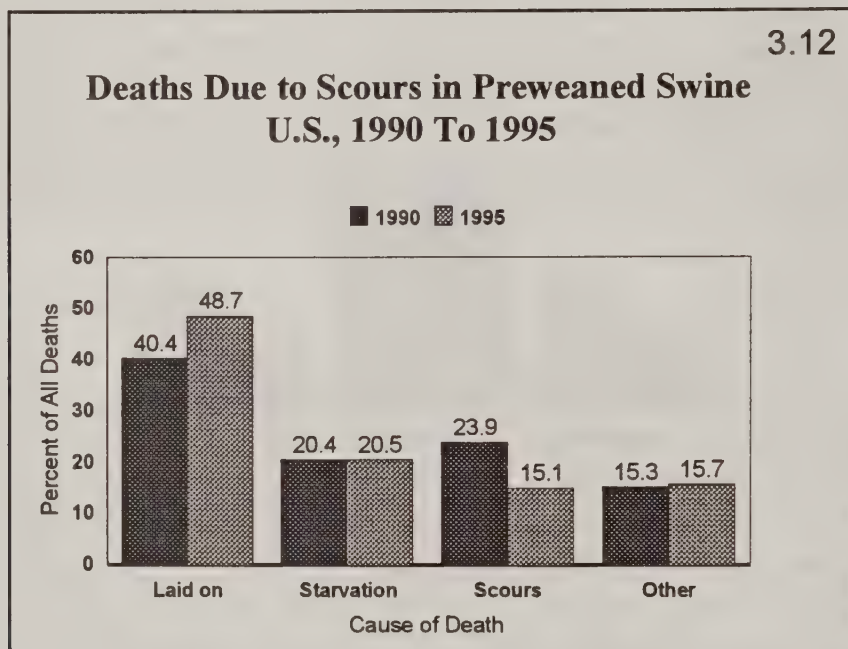
“long-duration of occupancy” (Figure 3.5). The sample prevalence within a pen (i.e., 30 samples) was from 0.0% to 36.7%. The ability to produce the toxins that contribute to human disease was found in all the isolates. The conclusion from NAHMS COFE '94 was that O157:H7 is widespread geographically, but the prevalence of O157:H7 is low when compared to other pathogens.



Descriptive Epidemiology of Colibacillosis

Swine

Colibacillosis-type diseases were studied in national surveys of U.S. swine (USDA/APHIS/VS, 1997e). Diseases in U.S. swine operations that were attributed to *E. coli* were two to four times more prevalent than diseases that were attributed to *Salmonella* and *Actinobacillus* (Figure 3.10). Scours was associated with 25.1% and 15.0% of deaths in nursery swine in the U.S. in 1990 and 1995, respectively (Figure 3.11). Similarly, scours was associated with 23.9% and 15.1% of deaths in preweaned swine in the U.S. in 1990 and 1995, respectively (Figure 3.12).



While the proportion of operations that attributed deaths in preweaned and nursery swine to scours decreased from 1990 and 1995, the proportion of operations that attributed deaths in grow/finish swine to scours increased (**Figure 3.13**).

A study to determine whether or not *E. coli* O157:H7 is present in the U.S. market hog population was conducted as part of the NAHMS Swine 95 survey. A total of 4,229 swine fecal samples collected from 152 randomly selected pork operations in the 6 top swine-producing states were tested for *E. coli* O157:H7, and none were positive (USDA/APHIS/VS, 1996).

Conclusion

Many previous reports of the prevalence of *Salmonella* and *E. coli* O157:H7 infections in U.S. livestock frequently have been restricted to localized geographic regions. One advantage of epidemiological studies by the NAHMS is that the studies are designed to provide national estimates of the prevalence of various pathogens. Infections by *Salmonella* and *E. coli*, or diseases related to these two pathogens, were detected at various levels on dairy, feedlot, and swine operations in the U.S. The prevalence of *Salmonella* shedding in dairy calves and in swine was higher in larger herds. The prevalence of *E. coli* O157:H7 shedding in dairy cows was also higher in larger herds. This suggests that herd-size as a risk factor for pathogen shedding, along with management factors associated with herd size, should be investigated further. Although the prevalence of antibiotic resistance was not a part of the studies reported here, the National Antimicrobial Resistance Monitoring System - Enteric Bacteria, has been organized to conduct surveillance for resistance in these two pathogens as well as others (Tollefson, 1998).

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Epidemiology of Antimicrobial Resistance in Selected Zoonotic Pathogens of Livestock and Poultry

Epidemiology of Antimicrobial Drug Resistance in *Salmonella*, *Escherichia coli* And Other Selected Pathogens of Livestock

Summary

This report briefly summarizes the epidemiology of antimicrobial drug resistance in animals in different countries, as presented at the WHO conference on "The Medical Impact of the Use of Antimicrobials in Food Animals" in October 1997 (World Health Organization, 1998).

Approximately 31 papers were presented by investigators from Australia, Belgium, Canada, China, Denmark, France, Germany, Russia, Scotland, Sweden, Switzerland, United Kingdom, and the United States. This description of the epidemiology of antimicrobial drug resistance in livestock is focused primarily on two important zoonotic pathogens, *Salmonella spp.* and *Escherichia coli*. In addition, the epidemiology of antimicrobial drug resistance in livestock was discussed briefly for the following pathogens: *Staphylococcus aureus*, *Serpulina hyodysenteriae*, *Campylobacter*, *Salmonella* Typhimurium DT104, and respiratory pathogens. Finally, resistance to several antimicrobials including vancomycin, streptogramins, and quinolones, is discussed.

Widespread resistance to old and to recently developed antimicrobial drugs is occurring in several pathogens that are commonly associated with diseases in animals and humans. In general, long-term trends in the prevalences of antimicrobial drug resistance were not available from many countries because many surveillance systems were organized only recently. Where available, data suggest that the prevalence of resistance of some infectious agents to some antimicrobial drugs used in livestock is increasing, and it is high already in some situations.

Definitions and Terminology:

multidrug resistant isolate -- a bacterial isolate that is resistant to more than one antimicrobial drug.

monodrug resistant isolate -- a bacterial isolate that is resistant to one antimicrobial drug.

R-type -- resistance type.

MIC -- minimum inhibitory concentration. MIC refers to the lowest concentration of an antimicrobial drug that will inhibit the growth of a bacterium *in vitro*.

prevalence of resistance-- the number of isolates of a specific bacterium that are resistant to a specific antimicrobial drug divided by the number of isolates that were tested (expressed as a percentage)

quinolones -- antimicrobial drugs (e.g. nalidixic acid) that are targets for DNA gyrase, an essential bacterial enzyme that is responsible for introducing superhelical twists into bacterial DNA.

fluoroquinolones -- antimicrobial drugs (e.g. enrofloxacin) that are derivatives of quinolones and are used in animals and humans. Fluoroquinolones are characterized by a fluorine atom at position 6 and an amine group at position 7.

glycopeptides -- a family of antimicrobial drugs.

group therapy -- a therapeutic regimen in which an antimicrobial drug is given to numerous animals simultaneously (e.g., via feed or water).

individual therapy -- a therapeutic regimen in which an antimicrobial drug is given to each animal separately (e.g., via injection).

Antimicrobial Resistance of *Salmonella*

Resistance of *Salmonella* spp. in the U.S.

The 1,041 specimens collected by the U.S.'s National Antimicrobial Resistance Monitoring System (NARMS) were from cattle (49.7%), swine (32.9%), chickens (12.0%), and turkeys (5.9%). Non-clinical isolates were acquired from the USDA's National Dairy Heifer Evaluation Project, the 1994 Cattle on Feed Evaluation, and the Food Safety Inspection Service during 1994-1995, and from an on-farm swine epidemiologic survey. The clinical isolates were selected randomly from the reference database of the National Veterinary Services Laboratory. Of these 1,041 baseline animal isolates that were tested for resistance, 59.6% were resistant to no (i.e., were susceptible to all) antibiotics, 11.8 % were resistant to one antibiotic, and 13.5% were resistant to two antibiotics (Tollefson et al., 1998).

The prevalences of resistance among *Salmonella* isolates were 34% for tetracycline, 28% for sulfamethoxazole, 13% for ticarcillin and ampicillin, 8% for neomycin, and 7% for piperacillin. The six resistant serotypes that were represented were *S. Derby*, *S. Typhimurium* variety Copenhagen, *S. Typhimurium*, *S. Agona*, *S. Cholerasuis*, and *S. Hadar*.

Resistance of *Salmonella* spp. in France

During the years 1994 and 1995, 15,878 *Salmonella* isolates were tested for resistance, of which 3,962 isolates were from animals (Brisabois et al., 1997). Of the 3,962 isolates from animals, 1,181 (29.8%) were from bovine and 2,438 (61.5%) were from poultry. Among the multiresistant or monoresistant *Salmonella*, eight resistant serotypes were found. These serotypes were *S. Typhimurium*, *S. Enteritidis*, *S. Virchow*, *S. Newport*, *S. Hadar*, *S. Saintpaul*, *S. Montevideo*, *S. Infantis*, and *S. Regent*. The prevalence of resistance was 63.7% for the bovine isolates and 33.6% for the poultry isolates. The prevalence of resistance in the 1,790 isolates from the environment was 34.2% (n = 613). A high prevalence of resistance to ampicillin, streptomycin, chloramphenicol and tetracycline was found (Brisabois et al., 1997). Serotype *S. Typhimurium*, the most prevalent antibiotic resistant serotype among the bovine isolates, represented 94.0% of all bovine *Salmonella* isolates that were resistant. The prevalence of resistance among all *S. Typhimurium* was 91.0%. There have been two observed changes in antimicrobial resistance since monitoring of *Salmonella* began in France around 1997: (1) a decrease in monoresistant isolates, and (2) an increase in multiresistant isolates towards four to five antibiotics, including a major phenotype referred to as R-type ACSSuT (ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline).

Resistance of *Salmonella* spp. in Sweden

Salmonella Typhimurium and *S. Dublin* are isolated from production animals only sporadically in Sweden. Thus, Sweden's surveillance for antibiotic resistance of *S. Typhimurium* and *S. Dublin*, undertaken first in 1976, is mostly for humans (Franklin, 1997). Generally, the prevalence of resistant *S. Typhimurium* isolated from animals has decreased since 1976. All serotypes except *S.*

Typhimurium and *S. Dublin* isolates were susceptible to “modern quinolones, trimethoprim-sulphonamides, neomycin and gentamicin.” The low prevalence of resistant *Salmonella* isolates was attributed to the highly restricted use of antimicrobials as an intervention for *Salmonella* infections in animals. Methods other than antimicrobials are used to eliminate *Salmonella* infections in animals in Sweden.

Resistance of *Salmonella* spp. in Russia

Surveillance for antimicrobial resistance in the USSR began in 1979 and continued at least through 1991 (Panin et al., 1997). In the mid-1980s, the susceptibility of 17,134 *Salmonella* isolates was determined. The *Salmonella* serotypes that have been surveilled are *S. Typhimurium* and *S. Cholerasuis* in pigs and *S. Typhimurium*, *S. Dublin*, and *S. Enteritidis* in cattle. Many isolates from pigs and cattle were resistant to chloramphenicol, tetracyclines, and aminoglycosides. The prevalence of resistance of *Salmonella* isolates from piglets was 20% to 48% for chloramphenicol, 31% to 68% for tetracyclines, and 35% to 40% for neomycin, each range being dependent on factors such as geographic region.

Trends in prevalence of resistance to chloramphenicol, tetracyclines, and aminoglycosides have been recorded in Russia since 1979 (Panin et al., 1997). The trends generally show an increasing prevalence of resistance, regardless of the specific microbe and the antibiotic. The sources of specimens and laboratory methods used from year to year should not be assumed to have been consistent. Chloramphenicol: The prevalence of resistance to chloramphenicol by *Salmonella* isolates from swine abruptly increased from 11.3% in 1979 to 74.6% by 1991 (Panin et al., 1997). Similarly, the prevalence of resistance to chloramphenicol by *Salmonella* isolates from calves increased from 30.3% in 1979 to 61.0% in 1991. Tetracyclines: The prevalence of resistance of *Salmonella* isolated from swine was somewhat stable at 55 to 60.0% for tetracyclines between 1979 and 1991, respectively. However, the prevalence of resistance of *Salmonella* isolated from calves has increased from 37.1% to 58.7% for tetracyclines. Aminoglycosides: The prevalence of resistance of *Salmonella* isolated from swine was 49.0% to 55% for aminoglycosides between 1979 and 1991. The prevalence of resistance of *Salmonella* isolated from calves was 45.0% to 48%.

Panin et al. (1997) suggested that reductions in the frequency of resistance between 1991 and 1998 were explained by decreased manufacturing of antimicrobial drugs in Russia, decreased importation of antimicrobials, and thus decreased use of antimicrobials in livestock production.

Antimicrobial Resistance of *Escherichia coli*

Resistance to *Escherichia coli* in Canada

E. coli isolates are becoming increasingly resistant to some antimicrobials that have been recommended to control *E. coli* (Fairbrother, 1999). A detailed epidemiologic study of resistance of *E. coli* was reported from Canada (McEwen et al., 1997). This observational study of Canadian farms was done to determine the statistical associations between antimicrobial usage in pig production and antimicrobial resistance among fecal *E. coli* isolates of finisher pigs. Finisher

pigs were selected as the study population because of the proximity of their ages to age-at-slaughter. It was assumed that enteric bacteria from feeder pigs were the source of contamination of carcasses. Fresh fecal samples were obtained twice from finisher pigs on each farm.

Multivariate logistic regression analysis was used to test the hypothesis that antimicrobial usage was associated with increased risk of resistance to *E. coli*. The dependent variables were the prevalences of resistance to the respective drugs (i.e., ampicillin, carbadox, gentamicin, nitrofurantoin, spectinomycin, sulfasoxazole, and tetracycline) at break-point concentrations.

The prevalences of *E. coli* resistance to ampicillin, carbadox, gentamicin, nitrofurantoin, spectinomycin, sulfasoxazole and tetracycline were 29.0%, 3.5%, 0.6%, 27.0%, 28.0%, 38.0% and 70.0 %, respectively. This resistance was relatively consistent over the two sampling periods, except for nitrofurantoin and tetracycline resistance. One possible explanation is that two farms began using tetracycline and furazolidone in rations of grower pigs immediately prior to collection of the first set of fecal samples.

The results of McEwen's study were as follows:

1. The risk of ampicillin resistance among *E. coli* was significantly increased with the practice of adding any antimicrobials to weanling rations, tetracycline to grower-finisher rations and penicillins to nursing sow rations.
2. Addition of carbadox to weanling rations was the only significant risk factor in the carbadox resistance model.
3. Similarly, the practice of administering individual treatments of gentamicin to piglets was the only significant factor in the gentamicin resistance model.
4. The risk of nitrofurantoin resistance was increased on farms that added any antimicrobials to weanling rations, but no other factors were significant in the nitrofurantoin resistance model.
5. The risk of spectinomycin resistance was associated with addition of any antimicrobial to grower-finisher rations.
6. The risk of sulfasoxazole resistance was associated with the addition of tetracyclines to grower-finisher rations only.
7. In the case of tetracycline resistance, addition of any antimicrobial to weanling pig rations, and addition of tetracycline to grower-finisher rations were associated with significantly increased risk of resistance.
8. Adding antimicrobials to the ration (i.e., ration therapy, ration medication) was associated with some form of resistance in most regression models, and the effect of ration therapy apparently over-shadowed the effects of individual-animal antimicrobial therapy.
9. Ration therapy of one type or another was significant in all models except the gentamicin resistance model; however, gentamicin was the only drug used exclusively for individual-animal antimicrobial therapy in the study population.
10. Tetracycline and ampicillin resistance were significantly more prevalent on farms where tetracycline and penicillin were used for group therapy, when compared to farms that used these drugs for individual-animal therapy only. Seemingly, individual-animal therapies had less impact on resistance than therapy via the ration.

Resistance of *Escherichia coli* in Sweden

Investigations of antimicrobial resistance of *E. coli* were done in Sweden to document trends in resistance. Most of the isolates of *E. coli* originated from herds in which there were pigs with diarrhea (Franklin, 1997). The frequency of resistance of *E. coli* isolates from pigs did not change dramatically in Sweden between 1981 and 1994 (Franklin, 1984; Franklin, 1997). Resistance to streptomycin decreased slightly and the usage of streptomycin decreased during the same time period by 80.0%. Resistance to tetracyclines is still common. The number of isolates resistant to trimethoprim-sulfa was considered to be unexpectedly high from 1981 through 1982 (9.0%), although trimethoprim-sulfa had been used only for 6 or 7 years in Sweden.

Resistance of *Escherichia coli* in Russia

The prevalence of resistance of more than 17,000 *Escherichia* isolates from calves in Russia in the mid-1980's was 20% to 68% for chloramphenicol, 36% to 87% for tetracyclines, and 29% to 57% for neomycin (Panin et al., 1997). The prevalence of resistance to chloramphenicol by *Escherichia* isolates from swine abruptly increased from 9.4% in 1979 to 62.1% by 1991. Similarly, the prevalence of resistance to chloramphenicol by *Escherichia* isolates from calves increased from 42.2% in 1979 to 65.6% in 1991. The trends show that the prevalence of resistance of *Escherichia* isolates from swine was stable at 60% to 65% for tetracyclines from 1979 through 1991. However, the prevalence of resistance of *Escherichia* isolates from calves increased from 43% to 73.4% for tetracyclines from 1979 through 1991 (Panin et al., 1997).

Resistance of *Escherichia coli* in the U.S.

While data about the prevalence of resistance of *Escherichia coli* from the U.S.'s (NARMS) - Enteric Bacteria is just beginning to become available, results of several other studies have been reported. The prevalence of resistance of *Escherichia coli* to trimethoprim-sulfamethoxazole was 39% for isolates from swine, 46% for isolates from cattle, and 42% for isolates from both (Hariharan et al., 1989; National Research Council, 1998). The prevalence of resistance of these same trimethoprim-sulfamethoxazole resistant, *Escherichia coli* isolates to tetracycline, neomycin, ampicillin, and nitrofurans was 98%, 80%, 74% and 30%, respectively. The prevalence of resistance of *Escherichia coli* from calves with enteritis was 3% to 95% for 10 different antimicrobial drugs in one study (Fairbrother et al., 1978; National Research Council, 1998). In a later study, the prevalence of resistance of *Escherichia coli* from calves with enteritis was 0% to 94% for the same 10 antimicrobial drugs (Coates et al., 1980; National Research Council, 1998).

Antimicrobial Resistance of Other Pathogens

(i.e., pathogens other than those associated with salmonellosis and colibacillosis)

Mastitis

Sweden has done surveillance on antimicrobial resistance of disease agents other than those of salmonellosis and colibacillosis. *Staphylococcus aureus* has surpassed *Streptococcus agalactiae* as the major cause of bovine contagious mastitis (Stewart, 1999). The cause-specific morbidity for mastitis due to *S. aureus* was 25% in Sweden (Franklin, 1997). About 5% to 10% of older and recent *S. aureus* isolates in Sweden are resistant to penicillin, due to their ability to produce penicillinase (Franklin, 1997). Methicillin-resistant *S. aureus* isolates have not been detected in dairy cows in Sweden. The low prevalence of penicillinase-producing isolates in Sweden may be explained by the therapeutic regimen for mastitis. Dry-cow therapy with antibiotics is used only in cows with a history of clinical mastitis during lactation. The antibiotic therapy is aimed directly at the causative bacterial species, and penicillin is never given to cows that are infected with penicillinase producing staphylococci.

Swine Dysentery

Swine dysentery, one of several bloody scours of swine, is caused by the spirochaete *Serpulina hyodysenteriae* (Glock, 1999). Parenteral therapy for swine dysentery may be followed by in-feed therapy or in-water therapy. Because swine dysentery may persist in affected herds, continuous, or at least repetitive therapy, is used to manage the disease. The antimicrobials used in the U.S. are bacitracin, carbadox, gentamicin, lincomycin, sodium arsanilate, tiamulin, tylosin, and virginiamycin. Dimetridazole and ipronidazole are prohibited as therapy against swine dysentery in the U.S. In Sweden, the MICs for *Serpulina hyodysenteriae* were lowest for carbadox, tiamulin, and Ipronidazole, and were highly variable for tylosin (Franklin, 1997).

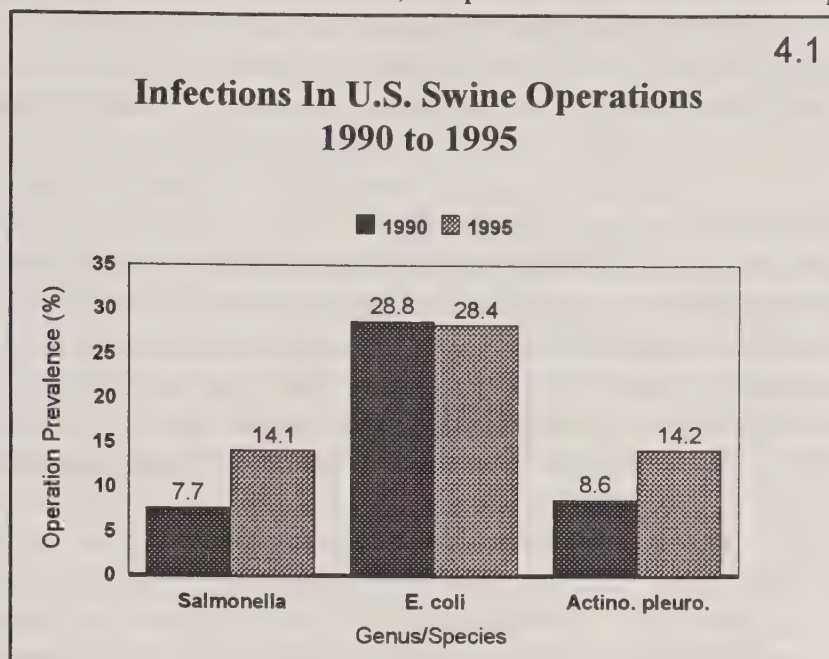
Campylobacteriosis

Campylobacter jejuni and *Campylobacter coli* are associated with diarrheal disease in cattle, sheep, goats and humans (Marshall, 1999). In Sweden, the prevalence of fluoroquinolone-resistant *Campylobacter jejuni* from chickens was less than 5.0%, while about 30.0% of human isolates were fluoroquinolone-resistant (Berndtsson et al., 1996; Sjogren et al., 1993). Some investigators have concluded that chickens may not be the primary source of fluoroquinolone-resistant, *Campylobacter* infections in humans in Sweden because the fluoroquinolone usage in chickens in Sweden was low (Franklin, 1997). All *Campylobacter* isolates from chickens were sensitive to erythromycin.

Respiratory Pathogens

Pneumonia in calves and pigs is associated with *Pasteurella haemolytica*, *Pasteurella multocida*, *Actinobacillus pleuropneumoniae*, and *Haemophilus somnus*. The operation prevalence of diseases that are related to *Actinobacillus pleuropneumoniae*, as reported by swine producers in the U.S., nearly doubled between 1990 and 1995 (**Figure 4.1**). In Sweden, these pathogens are sensitive to the beta-lactam antibiotics (e.g., penicillin, ampicillin), which are the premier antimicrobials for respiratory infections in pigs, calves, and sheep (Franklin, 1997). Beta-lactamase producing respiratory pathogens have not been isolated from production animals in Sweden (Franklin, unpublished material), and resistance of respiratory pathogens to other

antibiotics is rare in Sweden. In other countries, the prevalence of resistance to penicillin is higher



because of beta-lactamase production (Franklin, 1997).

Novel Antimicrobial-Resistant Pathogens

Salmonella Typhimurium DT104

The primary reservoir of *S. Typhimurium* DT104 is cattle, but the infection has been diagnosed in sheep, goats, pigs, horses, chickens and turkeys (Wall, 1997). One plasmid profile type, characterized by a single plasmid of approximately 60 megadaltons, accounts for most of the increase in both animal and human reports of *S. Typhimurium* DT104 of R-type ACSSuT (ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracyclines) (Threlfall et al., 1994). An increasing incidence of a multidrug resistant strain of *S. Typhimurium* DT104 in humans was reported in the UK (Threlfall et al., 1994). In 1996 more than 95.0% of *S. Typhimurium* DT104 isolates from humans received by the Public Health Laboratory Service (PHLS) Laboratory of Enteric Pathogens were R-type ACSSuT (CDR, 1997). Multidrug resistant *S. Typhimurium* DT104, with R-type ACSSuT, is now the second most prevalent *Salmonella*, after *Salmonella* Enteritidis PT4, in humans in England and Wales. Isolates of DT 104 that were referred to the PHLS Laboratory of Enteric Pathogens increased from 259 in 1990 to 2,873 in 1994, to 3,837 in 1995, and to 4,006 in 1996 (CDR, 1997).

S. Typhimurium DT104 with R-type ACSSuT is also present in animals and humans in the U.S. For those National Antimicrobial Resistance Monitoring System - Enteric Bacteria (NARMS-EB) isolates from animals, 14 of 137 (10.2%), 45 of 429 (10.5%), and 58 of 328 (17.7%) *S. Typhimurium* isolates were R-type ACSSuT in 1995, 1996 and 1997, respectively (Akkina et al., 1999). Of these *S. Typhimurium* R-type ACSSuT isolates, the proportion that were also phagetype DT104 was 64% in 1995, 22.2% in 1996 and 63.8% in 1997. In the NARMS-EB

study of human isolates, 103 of 306 (34%) and 112 of 321 (34.9%) *S. Typhimurium* isolates were R-type ACSSuT in 1996 and 1997, respectively (Glynn et al., 1998). For the 1996 human isolates, thirteen of the 103 R-type ACSSuT isolates were phagetyped and 85% were DT104, or they were part of the DT104 complex (i.e., other closely related definitive types or closely related untypeable isolates).

The emergence of human and animal isolates of DT104 with decreased susceptibility to ciprofloxacin was preceded by the licensing in the UK in November 1993 of enrofloxacin, a fluoroquinolone used for therapy in all species and for prophylaxis in poultry, calves and pigs (Wall, 1997). Since 1994, isolates with decreased susceptibility to ciprofloxacin (and trimethoprim) have appeared. In 1995, 6.0% of isolates were resistant to ciprofloxacin at MIC:0.25-0.5mg/L, and 27.0% of isolates were resistant to trimethoprim at MIC: >16mg/L (Threlfall et al., 1996). The incidence of ciprofloxacin resistance increased farther in 1996.

During 1994 and 1995, a case-control study was undertaken to investigate risk factors for DT104 infections in cattle in the UK. A case was defined as a farm with one or more symptomatic cattle infected with multidrug resistant *S. Typhimurium* DT104, and a control was defined as a farm selected at random on which no *S. Typhimurium* DT104 infected cattle had been identified. The risk factors identified were: (1) introduction of new stock to the herd, (2) no isolation facilities, (3) stress of calving, and (4) spread of infection by birds and feral cats (Evans, 1996). There was an increased risk of disease when cattle were housed, possibly indicating that persistently contaminated buildings may be a source of infection. Purchasing cattle from dealers, where there is more mixing of stock and thus a greater opportunity for spread of infection, was a greater risk than purchasing cattle directly from other farms (Evans, 1996). Widespread contamination of the environment, equipment, and vehicles was common in the early stages of herd infection. Human cases are often found on farms with infected animals (Wall et al., 1995). The strain has also been identified in domestic pets. Chronic carriage of DT104 for more than 14 weeks has been described in cats (Wall et al., 1995; Wall et al., 1996).

Vancomycin-resistant enterococci

Vancomycin-resistant enterococci (VRE), also referred to as glycopeptide-resistant enterococci (GRE), were isolated from humans in Europe in 1986 and in the United States in 1987 (Goossens, 1997). VRE/GRE have become an important nosocomial infection, especially in the U.S. Glycopeptide-resistance among isolates from farm and pet animals has been found in Europe. The prevalence of *Enterococcus faecium* isolates with vanA-mediated glycopeptide resistance was 8.0% in horses, 8.0% in dogs, 7.0% in chickens, and 6.0% in pigs in Europe. There are few reports of GRE in animals in the U.S., and the reports that do exist involve a few host species only. Specifically, VRE/GRE were not detected in fecal samples of chickens and turkeys in Texas (Coque et al., 1996). Nevertheless, the reports that do exist suggest that VRE/GRE are rare in animals in the U.S. The variations in prevalence between Europe and the U.S. may be due to differences in research methodology, including the type of specimen and laboratory procedures (e.g., failure to use enrichment media). For example, a higher prevalence of carriers of vanA isolates in the intestinal tract was found when stools, rather than swabs, were cultured using enrichment procedures (Jordens et al., 1994).

The results of the Danish antimicrobial resistance monitoring program (DANMAP) have shown that VRE/GRE could be detected among *E. faecium* isolated from Danish pigs, broilers, and cattle from October 1995 to September 1996 (Wegener, 1997). The prevalence of resistance was 29.0%, 59.0%, and 0.0%, respectively, for each species. The preliminary analysis of data for 1997 did not show marked changes in prevalence from previous years.

E. faecium, of the vanA genotype, is the predominant VRE/GRE in livestock and domestic pets in Europe (Goossens, 1997; DeVriese et al., 1996). VanA genotypes have become normal flora in pigs and poultry. Thus, it is possible that organisms with vanA resistance genes may be introduced into humans via the food chain. These colonized humans may introduce the vanA genotypes to human hospitals. The transmission of vanA resistance in this pattern could explain the very high genetic variability of the VRE/GRE isolated from hospitalized human patients in Europe. There are no data to suggest that the situation is similar in the U.S. (Goossens, 1997).

Resistance of enterococci and avoparcin use

There are increasing concerns about the association between resistance of enterococci in animals and food to vancomycin and using avoparcin as a growth-promoter in animal feeds (Bager et al., 1997; Klare et al., 1995b; Aarestrup, 1995; Bates, 1994). Antimicrobials of the glycopeptide class have been used as therapy against infections with multiple, antimicrobial-resistant, Gram positive bacteria in hospitalized human patients (vancomycin) and as an animal feed additive to increase growth rate (avoparcin). Avoparcin has not been available in the U.S. and Canada, but it has been available in many other countries since 1975 (Witte et al., 1997). Avoparcin is used as a growth-promoter for broiler chickens, turkeys, pigs, beef and dairy cattle, calves, sheep, and goats in countries where it has been approved. It was estimated that 24.0 kg of vancomycin was used for human therapy in Denmark in 1994, and 24,000 kg of avoparcin (active compound) was used as feed additives for growth promotion in pig- and broiler production (Wegener, 1997).

The first indication that animals are a reservoir for VRE/GRE came from an analysis in Great Britain (Jordens et al., 1994; Bates et al., 1994). After the emergence of clinical VRE/GRE isolates in a human hospital in Oxford, and the detection of VRE/GRE in fecal samples of both hospitalized and non-hospitalized human patients (Jordens et al., 1994), an investigation of VRE/GRE from humans, farm animals and sewage samples was undertaken (Bates et al., 1994). The *E. faecium* isolates were ribotyped, and 14 distinguishable patterns were found. The different ribotypes suggested that the human hospital was an unlikely origin of the porcine VRE/GRE. In a separate investigation, glycopeptide-resistant *E. faecium* was found in manure from a pig farm and a broiler farm in Germany that fed avoparcin, but not in manure from a poultry farm that did not feed avoparcin (Klare et al., 1995a; Klare et al., 1995b). VRE/GRE were isolated from slurry of another pig farm that fed avoparcin. Cross-resistance to vancomycin, teicoplanin, and avoparcin was found, regardless of the ecological origin of the isolates (Klare et al., 1995a). VRE/GRE were not detected on 17 farms at locations in Germany that did not feed avoparcin (Klare et al., 1995b).

The results of a large study in Denmark in 1995 were similar to those in Germany, i.e., VRE were found in poultry fecal samples from six of eight conventional farms that fed avoparcin, but they were not found in poultry from six farms which did not use feed additives (Aarestrup, 1995). VRE were found not only in poultry and pigs, but also in horses, dogs, and cats during an investigation in Belgium (in 1995), even though avoparcin has not been approved for use in companion animals (DeVriese et al., 1996). This finding raises concerns about the inter-species transfer of VRE/GRE. VRE have been found in large quantities in the liquid medium from thawed poultry and turkey broilers (Aarestrup, 1995; Chadwick et al., 1996). VRE were found in lower quantities in samples of raw minced meat (Aarestrup, 1995).

The EU Commission in 1996 banned avoparcin as a growth promoter as of April 1, 1997 (Wegener, 1997c). Recognizing the lack of information about the relationship between resistance to enterococci and avoparcin use, the Commission chose to take a precautionary approach. The U.S. FDA prohibited the extralabel use of glycopeptides in food-producing animals in the United States as of 1997. The FDA's ruling was based on concerns that glycopeptides in food-producing animals would lead to increased risk of transfer of resistant organisms to humans and compromise human therapy (Anonymous, 1997b).

Resistance to streptogramins and virginiamycin

The antimicrobials of the streptogramin family are naturally occurring compounds that are isolated from *Streptomyces pristinaspiralis* (Barri et al., 1992). The streptogramin family is divided into groups A and B, and includes antimicrobials such as the mikamycins, the pristnamycins, the oestreomycins, and the virginiamycins (Le Goffic et al., 1985). Oral pristnamycin (Pyostacine) has been used in Europe for many years to manage staphylococcal infections (Barri et al., 1992).

Virginiamycin is approved by the FDA in the United States for use in chickens, turkeys, swine, and feedlot cattle (Zervos, 1997). Indications for use in chickens includes weight gain, prevention of necrotic enteritis caused by *Clostridium perfringens* and prevention of coccidiosis; in turkeys for weight gain and prevention of coccidiosis; in swine for weight gain and treatment and control of swine dysentery; and in cattle for weight gain and to decrease the incidence of liver abscesses. Virginiamycin is a combination therapeutic that is derived from virginiamycin M (streptogramin A-type) and virginiamycin S (streptogramin B-type) antibiotics.

Quinupristin/dalfopristin is a new streptogramin that has recently (i.e., 1997) completed phase III clinical trials in Europe and in the United States (Zervos, 1997). Quinupristin/dalfopristin is a combination therapeutic that is derived from pristnamycin IA and IIA, respectively. Quinupristin/dalfopristin is expected to be highly efficacious against serious VRE infections of humans.

The prevalence of resistance of *E. faecium* to quinupristin/dalfopristin was as high as 100% in isolates from turkeys in 3 large flocks in Michigan (Zervos, 1997).

Quinupristin/dalfopristin-resistant and gentamicin-resistant isolates from turkeys in different culture groups were typed molecularly using pulsed field gel electrophoresis (PFGE) to search for

identical clones. The identical nature of the clones suggested that the isolates had spread among turkeys in the flocks (Donabedian et al., 1995). Higher prevalences of resistance to quinupristin/dalfopristin, ampicillin, and high-levels of gentamicin was found in older turkeys, which may be related to the longer exposure of older turkeys to antibiotics and to animals that are carriers of resistant isolates.

This study did not establish a link between resistant isolates in animals and in humans (Zervos, 1997). Nevertheless, because there is concern about a link between antimicrobials in animal feed and resistant isolates in humans, caution about the use of streptogramins in animals was encouraged by these investigators.

Fluoroquinolone-resistance of *Salmonella* spp. from cattle

France: Quinolones are synthetic antimicrobial agents that are used as therapy in humans and animals against *E. coli* and *Salmonella* infections. The four quinolones that have become available commercially to the French veterinary market are nalidixic acid, oxolinic acid, flumequine, and enrofloxacin (Brisabois et al., 1997). Enrofloxacin, a new generation fluoroquinolone, was approved in France for use in the bovine species in December 1991. Resistance to nalidixic acid, flumequine, oxolinic acid, and enrofloxacin was evaluated using isolates from bovine pathology specimens that were collected in 1995. Most of the 192 isolates of *Salmonella* that were evaluated were of the *S. Typhimurium* serotype. The prevalence of resistance to nalidixic acid was 13%, 6% to flumequine, and 9% to oxolinic acid. None of the isolates were resistant to enrofloxacin. Russia: The resistance of enterobacteria to fluoroquinolones was very low in Russia between 1993 and 1996. After 1996, the use of fluoroquinolones increased. Increased resistance of enterobacteria to fluoroquinolones has been found to be concurrent with increased use of fluoroquinolones (Panin et al., 1997).

Quinolone resistance of *Campylobacter* from poultry

The Netherlands: The predominant reservoir of *C. jejuni* and *C. coli* is thought to be poultry (de Mol, 1994), and *Campylobacters* are food-borne pathogens of humans. Flumequine has been used in veterinary medicine in The Netherlands since the early 1980s. Enrofloxacin was used first in veterinary clinical medicine in 1987, and ciprofloxacin was first used in 1988 (Jacob-Reitsma et al., 1994b). Enrofloxacin is used in broiler production to reduce vaccination problems and to combat respiratory problems due to *Escherichia coli* (Jacob-Reitsma et al., 1994b). No resistant isolates of *Campylobacter* veterinary isolates had been reported in The Netherlands between 1982 and the early 1990s (Endtz, 1991). By 1993 the prevalence of resistance of *Campylobacter* veterinary isolates to quinolones and fluoroquinolones (i.e., nalidixic acid, flumequine, enrofloxacin and ciprofloxacin) was 29.0% (181 of 617 isolates) (Pidcock, 1997). Thus, in 1991 Endtz et al. proposed that extensive use of fluoroquinolones in veterinary medicine in meat, poultry and milk production in The Netherlands contributed to the high frequency of fluoroquinolone-resistant *Campylobacters* isolated from humans (Endtz, 1991). Proof of transfer of antibiotic-resistant bacteria to humans via the complicated chain of events involved in poultry farming and food production was difficult. To determine whether broilers that were exposed to fluoroquinolones would provide an environment that would select for fluoroquinolone-resistant

Campylobacters, *Campylobacter*-colonized broilers were exposed to fluoroquinolones (Jacobs-Reitsma, 1994a). When the birds were slaughtered, fluoroquinolone-resistant *Campylobacters* were isolated from all colonized broilers that had been exposed to enrofloxacin. A reassessment of the use of fluoroquinolones in animal husbandry was recommended.

Sweden: The prevalence of resistance to enrofloxacin of 200 *C. jejuni* among 809 *Campylobacter* isolates that were from 6,297 slaughtered chickens in Sweden in 1992 and 1993 was only 4.5% (9 of 200 isolates). None of these flocks had undergone therapy with an antibiotic (Berndtsson et al., 1996). Cross resistance to other quinolones was not observed. The low prevalence of antimicrobial resistance in chickens was attributed to the restricted use of these quinolones in poultry production in Sweden.

Spain: It has been suggested that, since enrofloxacin was licensed for use in veterinary medicine in Spain in 1990, the increased use of enrofloxacin, flumequine and other quinolones has directly influenced the number of nalidixic acid-resistant *Campylobacters* (Velaquez et al., 1995). The prevalence of resistance has been correlated with dietary concentrations of quinolones, i.e., the prevalence of nalidixic acid-resistant *Campylobacters* increases as the concentrations of quinolones in poultry diets approaches the concentrations of quinolones that are used in the laboratory to select resistant isolates of *Campylobacters* (Velaquez et al., 1995).

United Kingdom: Enrofloxacin was not approved for veterinary use in the United Kingdom (UK) until November 1993, and “little” was used prior to January 1994. Thus, the UK has been referred to as a “control” country to assess the effects of veterinary use of fluoroquinolones on the emergence of fluoroquinolone-resistant, foodborne pathogens (Piddock, 1997). However, it is necessary to distinguish between poultry of UK- and non-UK origins, because much of the poultry consumed in the UK is imported from Europe. A study was done in the UK in 1993-1994, prior to licensing of enrofloxacin there, to assess the effect of veterinary use of fluoroquinolones on the emergence of fluoroquinolone-resistant *Campylobacters* (Gaunt et al., 1996). To do this study, 64 chickens of UK-origin and 50 chickens of non-UK origin were purchased from local supermarkets. The prevalence of *Campylobacter* in the chickens of UK-origin was 57.8% (37 of 64), and only one (2.7 %) of the 37 isolates was resistant to ciprofloxacin. The prevalence of *Campylobacter* in the chickens of non-UK origin was 52.0% (26 of 50), and seven (27.0 %) of the 26 isolates were resistant to ciprofloxacin. Whether there has been an increase in the numbers of ciprofloxacin-resistant *Campylobacters* isolated from UK-bred chickens, now that enrofloxacin has been approved, has not been shown yet; however, the numbers of resistant *Campylobacters* in the one localized area in the UK is increasing.

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Strategies to Reduce Antimicrobial Resistance in Food Animal Agriculture

Strategies to Reduce Antimicrobial Resistance in Food Animal Agriculture

Summary

Limiting availability of antimicrobials, enhanced surveillance, and on-farm interventions (including prudent antimicrobial use and management practices) have been proposed as key strategies to reduce antimicrobial resistance in food animal agriculture. Improved, rapid diagnostic methods and accelerated development and approval of new antimicrobial drugs can also play an important role in preventing and controlling antimicrobial resistance. This report describes the essential characteristics of a surveillance system for antimicrobial resistance and briefly reviews recently organized surveillance systems in the U.S., France, and Sweden. In addition, management practices that can decrease the need for antimicrobial use on the farm are explored. Examples of management practices that decrease the need for antimicrobials are the use of vaccines, probiotics, immune enhancers, good husbandry practices, and biosecurity. According to data from the USDA's National Animal Health Monitoring System (NAHMS), enhanced use of health management practices could reduce the requirements for antimicrobial drugs that are used for therapeutic purposes on U.S. swine, dairy, and beef operations. Some specific results of NAHMS' health management data were: (1) Only 32% of calves received the recommended volume of colostrum during the first feeding. (2) The immunoglobulin concentration was less than ideal in approximately 67% of the 2,177 dairy calves sampled. (3) Proper protection against respiratory pathogens may have been inadequate in as many as 86% of beef calves in the U.S. at the time of sale in 1997, based on the frequency of vaccination. Educating animal producers and veterinarians concerning these strategies to prevent and control antimicrobial resistance is an essential component for the strategies to be effective.

Introduction

Strategies to identify and reduce antimicrobial resistance in food animal agriculture should include interventions at all levels, from global to national and local, including the individual farm and animal. National laws and regulations pertaining to antimicrobial licensure and compliance can effectively limit availability to antimicrobials (WHO, 1997). National laws and regulations can also be used to stimulate new antimicrobial drug discovery and to accelerate new drug approval. Monitoring and surveillance of antimicrobial resistance in food animals is an intervention activity that should operate at all levels, global, national and local. Surveillance needs to track both resistant organisms and antimicrobial use. A surveillance system to monitor the prevalence of resistant organisms should provide the necessary information to determine the magnitude of the problem and evaluate the impact of interventions aimed at decreasing resistance. A database system to collect information on amount and methods of antimicrobial use in food animal agriculture is also needed. Ideally, the information on antimicrobial use should be able to relate back to the information on resistance. It is important that these database systems be able to track trends over time and can also harmonize with both human and international surveillance systems.

In addition to limiting availability to antibiotics, and monitoring and surveillance programs, on-farm interventions at the local level may reduce the risk of antimicrobial resistance. On farm interventions include prudent use of antimicrobials and implementation of management practices

which decrease the need for antimicrobials. Prudent use of antimicrobials is defined as use in a manner that promotes their effectiveness yet minimizes bacterial resistance development (Apley et al., 1998). Development of new diagnostic methods to quickly differentiate viral from bacteria infections, identify the specific viral or bacterial infection, and determine drug susceptibility of the organism, can facilitate prudent use of antimicrobials (Huovinen, 1998). Examples of management practices that decrease the need for antimicrobials are the use of vaccines, probiotics, immune enhancers, good husbandry practices, and biosecurity.

Limiting Availability to Antimicrobials

Recent controversies surrounding the approval of fluoroquinolones in food animals has brought the process of antimicrobial drug approval for food animals under scrutiny. In January, 1999, the FDA published in the Federal Register a discussion paper titled “A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals”. The proposed regulations are aimed at reducing antimicrobial resistance development in zoonotic, foodborne pathogens. The Framework outlines the following five components of how to evaluate and minimize the potential human health effects of uses of antimicrobial drugs in food-producing animals:

- 1) assess the effect of proposed uses on human pathogen load;
- 2) assess the safety of proposed animal uses of drugs according to their (or related drugs) importance in human medicine and the potential human exposure to resistant bacteria acquired from food-producing animals that are human pathogens or that can transfer their resistance to human pathogens;
- 3) assess pre-approval data showing that the level of resistance transfer from proposed uses of drugs, if any, will be safe;
- 4) establish “resistance” and “monitoring” thresholds to ensure that approved uses do not result in resistance development in animals or transfer to humans above the established levels; and
- 5) establish post-approval studies and monitoring.

Surveillance of Antimicrobial Resistance

The aims of a resistance monitoring program are described in the World Health Organization’s report on the “Medical Impact of the Use of Antimicrobials in Food Animals” (WHO, 1997). A resistance monitoring program should gather information to promote prudent and judicious use of antimicrobials in livestock production, enable informed decision-making by national regulatory institutions, guide prescription practice, encourage standardization of laboratory techniques for monitoring, identify areas for more detailed investigation and promote collaboration.

The following characteristics of an ideal surveillance system are from the Workshop Report on Antimicrobial Resistance: Issues and Options, Institute of Medicine, 1998. An ideal system should:

- 1) be prospective, active, timely, and affordable;

- 2) provide accurate incidence rates and prevalence, which would in turn require both numerator and denominator information (e.g., the number of isolates tested and the number of resistant isolates), as well as a mechanism to permit exclusion of repeat isolates from the data pool;
- 3) include information that identifies organisms causing infection and those involved in colonization (i.e., the ability of a bacterium to remain at a particular site and multiply there);
- 4) gather data so as to permit categorization by region and locality, as well as to discriminate between animal species and clinically ill versus healthy animals;
- 5) gather information on antimicrobial use and treatment outcomes, especially treatment failure (the outcome of resistance);
- 6) be able to detect new resistance markers and therefore be dependent on standardized and reliable laboratory techniques, uniform criteria for determining resistance, appropriate specimens for culture, and adequate microbiologic validation;
- 7) be a national network representing all regions;
- 8) computerize all participating laboratories, regularly collect electronic data, process and report in ongoing fashion, and integrate all databases at the national level;
- 9) make surveillance data available to practitioners at the appropriate regional and local levels so that problems at these levels could be managed appropriately.

The Current U.S. Surveillance System for Antimicrobial Resistance in Animals

The current U.S. surveillance system for monitoring antimicrobial resistance of enteric bacteria in animals and humans is called the NARMS-EB (National Antimicrobial Resistance Monitoring System - Enteric Bacteria). The goals and objectives of the NARMS-EB monitoring program are to:

- 1) provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in *Salmonella* and other enteric organisms from animal and human populations;
- 2) facilitate the identification of resistance in animals as it arises;
- 3) provide timely information to veterinarians and physicians;
- 4) prolong the life span of approved drugs by promoting the prudent and judicious use of antimicrobics; and
- 5) identify areas for more detailed investigation.

Monitoring is currently targeted to *Salmonella* spp., *Campylobacter*, and *E. coli*. *Salmonella* isolates are collected from multiple sources: (1) clinical isolates submitted to the National Veterinary Services Laboratories from around the country, (2) isolates collected as part of NAHMS periodic national surveys, (3) isolates from other epidemiological studies, and (4) all *Salmonella* isolates from slaughter samples around the country. Isolates from three diagnostic laboratories, one each in Washington, California, and New York were added to NARMS-EB in 1998. Isolates are collected from the various sources mentioned above and susceptibility testing is then conducted at a central location, the USDA:ARS Richard Russell Research Center in Athens, GA. The USDA agencies involved in NARMS are APHIS, ARS and FSIS.

Surveillance of Antimicrobial Use in Animals

In the U.S., detailed records are not kept at point-of-sale for animal antimicrobial use, unlike for human antimicrobial use. Producers can obtain certain antimicrobials over the counter at farm supply retail outlets, and veterinarians most commonly obtain antimicrobials from a pharmaceutical firm representative. Information on sales from the pharmaceutical industry is mostly proprietary. Therefore, there is a significant lack of detailed information on the amount, potency and characteristics of antimicrobial use in animal agriculture. Such detailed information is a critical component in evaluating the impact of antimicrobial use on antimicrobial resistance.

Veterinary Services' NAHMS program can play an important role in obtaining information on antimicrobial use on the farm with the cooperation of producers. Future objectives for NAHMS surveys can include collecting information on antibiotic use practices. Information on which antibiotics are used, when, how, and under what guidance, could be obtained and national estimates calculated. In addition, if future NAHMS surveys will be able to link resistant isolates with use of antibiotics on a specific operation, risk factors for antibiotic resistance could be evaluated.

Future Goals for Surveillance in the U.S.

The current U.S. Surveillance system for monitoring antimicrobial resistance in animals has a national focus, however it does not have the ability to produce data on antimicrobial resistance at the local level, or the resources to examine more than a few pathogens. If it is important to have more locality-specific information, perhaps for specific species of animals and representing additional genera of bacteria, several avenues are available to gather such data. First, the existing system could be expanded to incorporate additional clinical isolates from diagnostic laboratories. Second, passive monitoring of clinical isolate resistance patterns could be implemented if a private sector company were to implement a service to collate data on veterinary isolate resistance patterns such as is available for human isolates. Third, another entity, perhaps public or from academia, could initiate a system to collate data on resistance profiles of animal isolates from diagnostic laboratories. The NAHMS program has a history of working with diagnostic laboratories in the past to collate data on accessions and diagnoses. Thus NAHMS may be an appropriate organization to provide leadership for the surveillance system should the third approach be appropriate (Personal communication, David A. Dargatz, USDA/APHIS/VS, 1999). Regardless of how the data are generated and collated it will be imperative that they be channeled into a single system, analyzed and interpreted and that feedback be provided to diagnostic laboratories, and health care providers (human and animal) in order to facilitate prudent antimicrobial use decisions.

Before a new system based on resistance data from veterinary diagnostic laboratories can be initiated, standardization of resistance testing methods among laboratories must be assessed. The USDA/APHIS/VS Centers for Epidemiology and Animal Health (CEAH) is planning a survey of diagnostic laboratories to collect data on the resistance testing methodologies in use and to determine how the results of testing are being stored (Personal communication, David A. Dargatz, USDA/APHIS/VS, 1999). The results of this survey will provide an assessment of

current feasibility and any changes which will be required, to improve standardization and facilitate data aggregation, before this type of surveillance system can be implemented.

Antimicrobial Resistance Surveillance Systems - International Perspective

Information from surveillance systems for antimicrobial resistance is necessary to evaluate even superficially the validity of reports of increasing prevalence of resistance to antimicrobial drugs. Surveillance systems explicitly for antimicrobial resistance will provide the best estimates of the prevalence of resistance. Such surveillance systems have been organized in France, Sweden, and as described above, in the United States.

France: The primary focus of systems that have been described in France is zoonotic salmonellosis. Since 1978, the National Veterinary and Food Research Centre (CNEVA) through the CNEVA-Paris and the CNEVA-Lyon has been monitoring the antibiotic resistance of *Salmonella* and observing the spread of multiresistant isolates of serotypes isolated from animals, especially from cattle and poultry operations, and from their environments (Brisabois et al., 1997). Isolates associated with epidemiological information are collected from a network of nearly 200 veterinary or food hygiene laboratories. An inventory of *Salmonella* serotypes and antibiotic resistance has been published every two years for more than twenty years. For epidemiological analysis of the serotypes and antibiotic resistance patterns, the isolates are subdivided according to their source:

- isolates from animal samples,
- isolates from food hygiene samples, including feedstuffs,
- isolates from environments, including animal production environments and the natural ecosystem.

During 1994 and 1995, 25,220 *Salmonella* isolates were collected by the CNEVA-Paris, and 15,878 were tested for antimicrobial susceptibility (Brisabois et al., 1997). Among the 25,220 isolates, 7,691 (30.5%) were from animals, 12,220 (48.5%) from food hygiene and 5,309 (21%) from environments.

Since 1982, the RESABO Network, a national veterinary network of 40 regional veterinary diagnostic laboratories, has monitored resistance to antimicrobials by common pathogenic bacteria from cattle, including *Salmonella* (Brisabois et al., 1997). Standardized diagnostic methods are used by the RESABO Network, which is managed by a central reference laboratory (CNEVA-Lyon). The RESABO network collects current data on antimicrobial resistance by veterinary isolates and analyzes isolates for specific mechanisms of resistance to antibiotics.

Sweden: Antibiotic resistance of *Salmonella* isolated from animals in Sweden has been surveilled since 1976, in accordance with WHO recommendations (Franklin, 1997). *Salmonella*, mostly *S. Dublin* or *S. Typhimurium*, are only sporadically isolated from production animals. Thus, surveillance in Sweden is primarily for purposes of human health.

Plans to Enhance Surveillance Systems for Antimicrobial Resistance In Europe

A comprehensive study of the prevalence of *Enterococcus faecium* resistance to avoparcin found the prevalence to be 59% in broiler chickens, 29% in pigs, and 0% in cattle (DIARMRP).

Vancomycin-resistant enterococci (VRE), usually of *E. faecium*, can be resistant to numerous antibacterials. It has been suggested that animals may be a source of human infections (Bates et al., 1994). Thus, the use of avoparcin in animals has gained attention. The apparent link between avoparcin use in animals and the occurrence of vancomycin resistant *E. faecium* in pigs and poultry was highlighted by the Danish Veterinary Laboratory (Anonymous, 1995a). The EU SCAN Committee (i.e., Scientific Committee for Animal Nutrition) concluded that there was insufficient evidence to conclusively link avoparcin therapy in animals and VRE in humans. Nevertheless, the EU Commission suspended sales of avoparcin in April 1997 and requested:

- 1) data on antimicrobial resistance, especially due to glycopeptides.
- 2) a surveillance program for antimicrobial resistance in animals.

Consequently, a new surveillance system involving the United Kingdom, Spain, France, the Netherlands, Denmark and Sweden is being developed specifically for *E. faecium*. Samples from pigs and poultry will be tested for resistance to avoparcin, avilamycin, virginiamycin, flavomycin, tylosin/spiramycin, and bacitracin.

This surveillance program is expected to provide information on the susceptibility of isolates of *E. faecium* from European countries with a variety of husbandry systems, climates and policies related to feed additives. The program is not in itself expected to answer the crucial question regarding potential risk to humans, but it is expected to be of great interest in association with other data on transfer of resistance between species.

On Farm Interventions

Improving prudent use of antimicrobials

The primary responsibility for improving prudent use lies with the veterinary organizations such as the American Veterinary Medical Association (AVMA), American Association of Bovine Practitioners (AABP), and the American Association of Swine Practitioners (AASP). These organizations can provide guidelines aimed at reducing unnecessary use and promoting use which will minimize antimicrobial resistance and maximize effectiveness of antimicrobials. In November 1998, the AVMA Executive Board approved a position statement and principles for judicious therapeutic antimicrobial use by veterinarians (Anonymous b, 1999).

Research into specific dose/duration regimens for specific antibiotics, rotating choices of antibiotics periodically and using combinations of therapy, and their impact on resistance development is needed. The private and university sectors need to be involved in this type of research. Clinical trials are needed to examine the effects of long-term, low-level antibiotic use, prophylactic use, and therapeutic use on antimicrobial resistance development. A monitoring program which can guide veterinary selection of appropriate antimicrobials based on

regional/local trends in resistance is also needed. Information from these studies should feed back into prudent use guidelines.

Veterinary Services can assist prudent use efforts by characterizing current use methods, identifying areas where change is needed, monitoring progress through recurring surveys, and monitoring the success of education programs. Veterinary Services can also take a more active role in education. Veterinary Services already collects, analyzes and interprets data related to animal health and the production of livestock. In order to maximize the impact of this research, Veterinary Services needs to become more involved in educating producers and practitioners concerning the findings.

Management Practices That Decrease the Need for Antimicrobials

Conceptual shifts in thinking are needed to address the problem of antimicrobial resistance. One potential shift in thinking is to better understand and actively manage the microbial ecology of the farm, promoting and protecting the “good” microorganisms, and minimizing the “bad ” microorganisms. Antimicrobials would then be used with a narrow focus only when needed and efforts would be made following antimicrobial therapy to restore a healthy, susceptible, microbial flora. Feedstuffs and management practices which promote a healthy microbial flora and a healthy immune system would be a priority.

Veterinary Services can play an important role in identifying management practices which promote animal health and productivity while minimizing antimicrobial use. NAHMS surveys can identify operations with low levels of resistance and identify which management practices are associated with low levels of resistance. Increasing use of vaccines has been proposed as a method to decrease antimicrobial use. This will require the widespread availability of highly efficacious vaccines that are easy to give at a reasonable cost. For many of the currently available vaccines, one or more of these criteria are perceived to be lacking. The Agricultural Research Service (ARS) can assist in this effort by conducting initial development of new vaccines or by conducting studies which show the cost effectiveness of existing vaccines. Development of vaccines is also a role of the biologics industry.

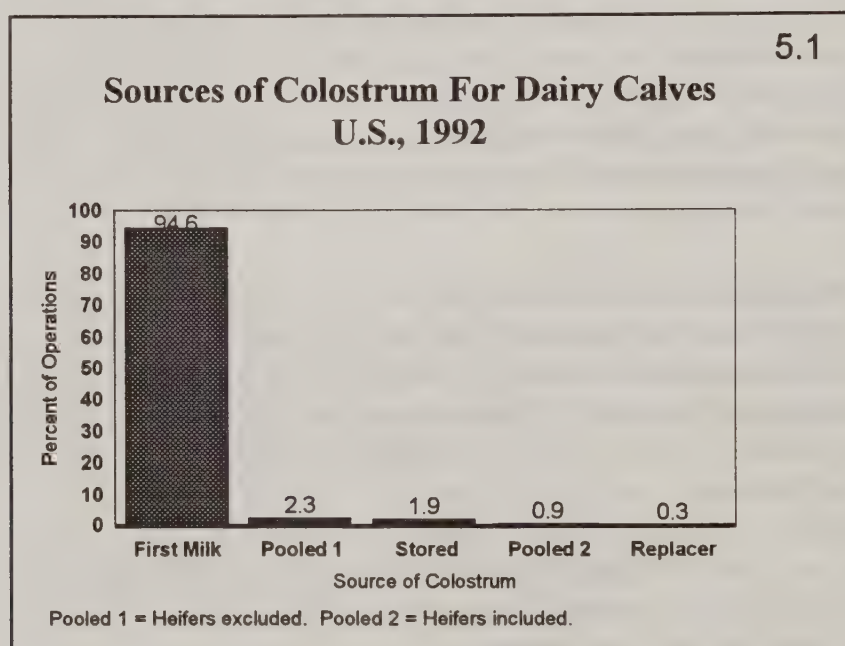
Development and use of immune modulators may help to reduce the need for antimicrobials. Attention to proper nutrition and adequacy of trace minerals in the diet are also key to an effective immune response in livestock. Research and development of probiotics, also known as competitive inhibitors, is being conducted by ARS. Research on cattle and swine probiotic products is currently underway at the ARS station in Texas. Several examples of potentially novel alternatives to using antimicrobials as growth promotants or prophylactics are currently under research/development by universities or private industry. These examples include: (1) avian antibodies for the prevention of *E. coli* infection in piglets and calves and for growth promotion in poultry and swine (Pimentel, 1999); (2) seaweed (*Ascophyllum nodosum*) meal to enhance immunity and for growth promotion in cattle, and (3) vitamin E supplementation in broiler diets to improve performance (Chung and Boren, 1999).

The application of more stringent biosecurity practices on operations, such as when new animals are introduced, may eliminate or reduce the risk of introduction of diseases that could require antimicrobial therapy. These practices may include: only buying animals from herds with known high health status; pre-arrival testing; and use of quarantine facilities. Practices to reduce feed and water contamination can also reduce disease risk.

Disease Prevention and Control Management Practices in the U.S.

Passive Immunity

Management factors that lead to inadequate natural and artificial immunity in animals may increase the demand for antimicrobial drugs on livestock operations. Colostrum is a newly born calf's most valuable source of protection against the early onset of disease. The duration of these protective antibodies in the serum of calves can be weeks to months. Results of the NAHMS

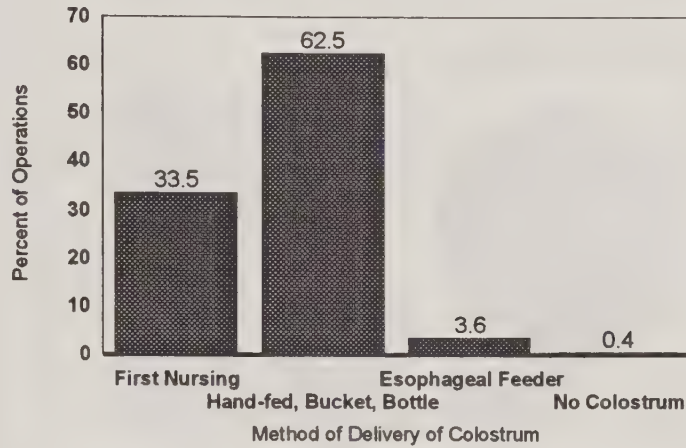


1992 National Dairy Heifer Evaluation Project (NDHEP) showed that calves on 95% of U.S. operations receive colostrum from their dam's first milking (USDA/APHIS/VS, 1993b) (**Figure 5.1**). Calves on nearly two-thirds of the operations were fed colostrum from a bucket, bottle, or esophageal feeder, all of which provide some assurance of the volume of colostrum being ingested by the calves (**Figure 5.2**). The remaining one-third of the calves received colostrum via first nursing, or did not receive colostrum.

Four quarts of colostrum is the recommended volume for the first feeding to prevent failure of passive transfer (Roussel et al., 1999). Only 32% of calves received 4 quarts or more during the first feeding (**Figure 5.3**). The immunoglobulin concentrations were less than 1,000 mg per dl in more than 40% of the 2,177 dairy calves sampled, and the concentration was unmeasurable (i.e. less than 620 mg per dl) in more than 27% of the calves (**Figure 5.4**). Twenty-two percent of all dairy calf deaths may be prevented by ensuring that calves consume adequate volumes of colostrum (USDA/APHIS/VS, 1993c). The volume of colostrum consumed by beef calves is

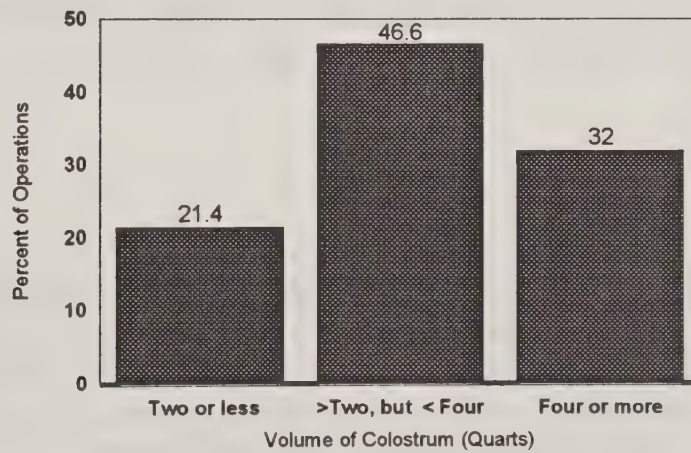
5.2

First Feeding Of Colostrum To Dairy Heifers U.S., 1996

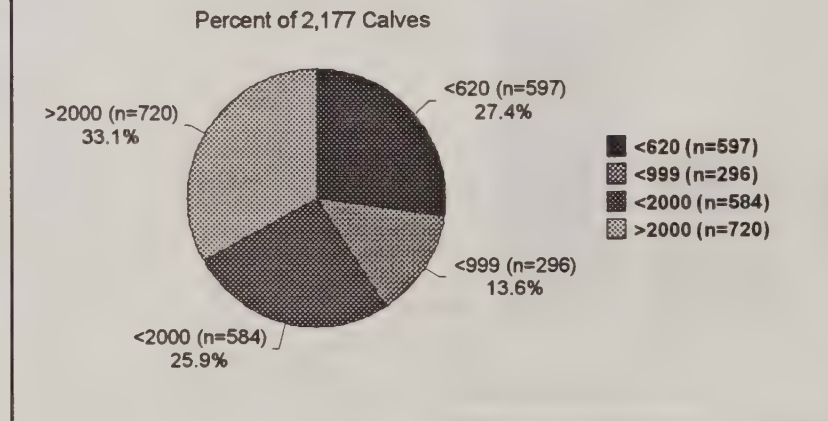


5.3

Volume of Colostrum Fed Manually To Dairy Heifers U.S., 1996



Immunoglobulin G (IgG) in Dairy Calves U.S., 1992



more difficult to measure than in dairy calves. However, a smaller volume is required to provide passive immunity in beef calves versus dairy calves, partly because the immunoglobulin concentration is greater in colostrum from beef cows (Roussel et al., 1999).

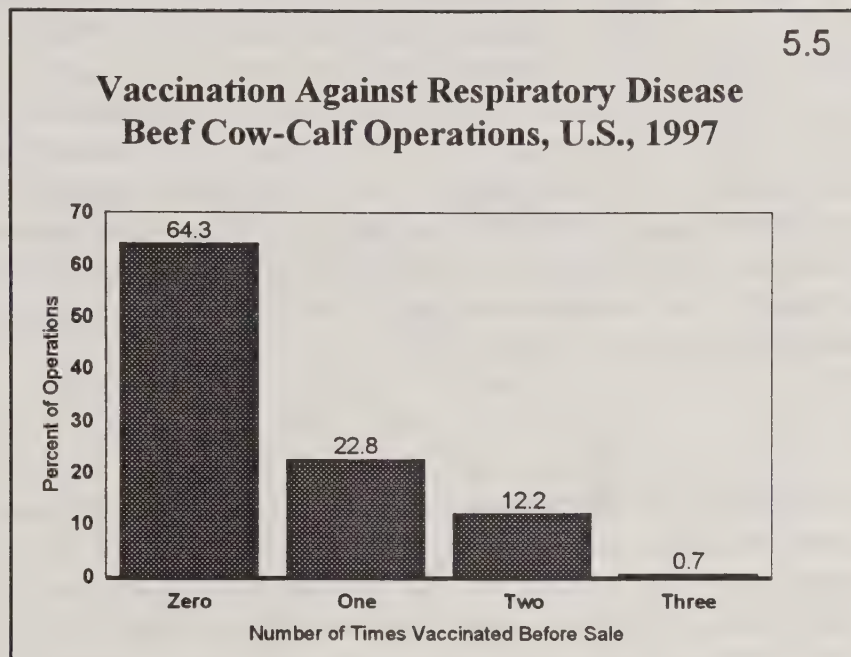
Increased use of antimicrobial drugs may be essential to protect dairy and beef calves with failure of passive transfer from bacterial infections, or from viral infections that are complicated by bacterial infections. Providing calves with adequate passive protection may reduce these deaths and decrease the demand for prophylactic and therapeutic antibiotics.

Active Immunity

Vaccination Frequency

Efficacious vaccines can provide calves with artificial immunity, if natural immunity has not been achieved via consumption of colostrum (Wren, 1997; Roth, 1997). More than 64% of beef calves were not vaccinated against respiratory disease prior to sale in 1997, and 22% were vaccinated only once (USDA/APHIS/VS, 1998) (**Figure 5.5**). Frequently two injections of a vaccine are recommended to stimulate the primary and anamnestic responses, both of which are essential for optimal immunoprophylaxis against disease. Thus, protection against respiratory pathogens at the time of sale may have been inadequate in as many as 86% of beef calves in the U.S. in 1997, based on the frequency of vaccination. Infectious bovine rhinotracheitis (IBR), bovine viral diarrhea (BVD) virus, and bovine respiratory syncytial virus (BRSV) are three pathogens associated commonly with the bovine respiratory disease complex (BRDC). Killed and modified-live versions of vaccines for these pathogens are available. Although revaccination within 60 days of the first vaccine is recommended by the manufacturers, only 28% to 29% of those producers who vaccinated against BRDC followed the manufacturers' recommendations.

Vaccination Timing



The effectiveness of vaccines is determined in part by the interval between vaccinations, in addition to the number of vaccines as described above. For operations that vaccinated calves for respiratory disease at least once, 36% vaccinated the calves at weaning, and 20% vaccinated after weaning, but prior to selling the calves. The stress and possible immune suppression that are coincident with weaning may sufficiently decrease the immunologic response to the vaccine to the point of being effective only marginally. Increased use of antimicrobial drugs may become essential to prevent or control what could be vaccine-preventable respiratory infections in beef calves prior to weaning.

Biosecurity

Minimizing the risk of introducing disease to an operation should be a relentless goal of all herd health programs. General principles of biosecurity such as restricted access of non-farm personnel, internal (versus external or purchased) replacements of livestock, and animal quarantine and/or isolation can be used to prevent the introduction of infectious diseases to farms. These practices can be used also to prevent animal-to-animal transmission of diseases, after a disease has been introduced to the farm. Both of these practices could contribute subsequently to the decrease in antimicrobial use (Sischo, 1997; Wren, 1998). Biosecurity practices on U.S. swine, dairy, and cow-calf operations were a part of the NAHMS studies between 1990 and 1997.

Swine Biosecurity

Slightly more than 40% of swine operations “restricted entry” into their operations to their employees only (USDA/APHIS/VS, 1992; USDA/APHIS/VS, 1995). Feed delivery personnel, livestock haulers, and other visitors were among non-employees who were permitted on those operations with “non-restricted entry”. Livestock haulers have been shown to be a potential risk

factor for inter-farm transmission of pseudorabies virus and could serve as a vehicle for other infectious agents for which antibiotics would be an appropriate intervention (Austin et al., 1993). Less than 2.0% of all U.S. swine operations required a footbath and less than 1.0% required a shower of feed delivery personnel and livestock haulers before they were permitted on the operation. Less than 3.0% of all U.S. swine operations required a footbath and less than 1.0% required a shower of visitors other than feed delivery personnel and livestock haulers, before they were permitted on the operation. Breeding females were never quarantined by 50% of operations, breeding males were never quarantined by 36%, and feeder pigs were never quarantined by 72% of the operations. More than 50% of the operations did not screen the health of breeding females and breeding males using biological specimens (e.g., blood) before admitting these animals to the operation. For feeder pigs, this percentage was 81%.

Dairy Biosecurity

According to the NDHEP, 46% of U.S. dairy operations brought cattle onto their operations during the 12 months prior to this 1991 survey (USDA/APHIS/VS, 1993a). Dairy cattle at virtually every stage of production (e.g., calves, dry cows) were brought onto the operations. More than 25% of the operations brought on either lactating cows and/or heifers. More operations quarantined calves and young heifers than other older cattle, but the operations that quarantined calves and young heifers represented only 27% of all operations that brought on calves and young heifers. In general, quarantines were used infrequently on dairy operations. Only 5% of the operations washed the cow's udder prior to birth of the calf, and only 46% of the operations applied an antiseptic to the navels of newborn calves. Feeding utensils were shared by calves on 84% of all operations, but the utensils were washed and/or sanitized from one calf to the next on 17.9% of the operations only. Close physical association between young and adult stock may promote transmission of some infectious diseases, e.g., paratuberculosis (Bungert 1997; Wren 1998). Young, preweaned calves had close physical contact with older, weaned calves on nearly 32% of the operations.

Beef Biosecurity

Brucellosis, bovine viral diarrhea (BVD), infectious bovine rhinotracheitis (IBR), and leptospirosis are infectious diseases that may cause significant reproductive losses in herds. Vaccines may be used to prevent these infections in animals currently in residence on the farm (Wren 1997). Vaccines may be used also as a biosecurity tool to reduce the risk of introducing the infections via herd additions. Less than one-third of producers that brought cattle onto U.S. beef operations required vaccination of females for brucellosis (USDA/APHIS/VS, 1998). Only 13% of operations adding new animals required vaccination for either BVD, IBR, or leptospirosis. Newly admitted animals that have not been vaccinated may be carriers of these pathogens, unless diagnostic tests have been used to confirm that they are free of disease. Less than one-third of producers that brought cattle onto U.S. beef operations required that the animals be tested for brucellosis prior to being admitted to the operation (USDA/APHIS/VS, 1998). No more than 4% of the operations that admitted new animals required that they be tested for BVD, Johne's disease, or bovine tuberculosis (TB) prior to being admitted to the operation. While the percentage for brucellosis is significantly higher than for BVD, Johne's, and TB, requesting

diagnostic tests to minimize the risk of disease transmission may not be the motive for this difference. Rather, the difference may be due to regulations related to interstate movement of animals.

Minimizing Antimicrobial Use - International Perspective

Although there has been general consensus that the prevalence of resistance is correlated closely with the prevalence of antimicrobial drug use, the epidemiologic evidence to support this belief has been lacking, until recently. According to the Finnish Study Group for Antimicrobial Resistance, the prevalence of resistance of group A streptococci to erythromycin increased from 5% in 1988 to 13% in 1990 (Seppala et al., 1997). This increase was correlated with a three-fold increase in consumption of erythromycin from 1985 to 1988. A nation-wide reduction in the consumption of erythromycin from 1991 to 1996 was followed by a decrease in the prevalence of erythromycin resistance from 16.5% in 1992 to 8.6% in 1996. It has been suggested that the correlation between the prevalence of resistance and erythromycin consumption provides a scientific basis for a permanent reduction in antimicrobial drug use in food animal production (Blaha, 1997).

There is substantial anecdotal evidence antimicrobial drug use is lower on healthy operations (Blaha 1997). Management practices that tend to be associated with the medical (versus financial) health of a swine operation are: (1) source herds, (2) all-in all-out pig flow, (3) group farrowing and transfer of closed groups, (4) matching based on health status, (5) specific pathogen free (SPF) animals, (6) and segregated early weaning (SEW). There is some evidence that SEW significantly reduces antibiotic use. A pork production system in which the objective is to completely eliminate antibiotics has been created by one Finnish food company. Consumption of antibiotics has been reduced by 70%, and more than 90% of the pigs are not exposed to antibiotics (Tuovinen et al., 1997).

Epidemiological studies (e.g., the NAHMS program) could play a significant role in verifying these anecdotal reports that specific management practices may significantly reduce antimicrobial use on farms (Blaha 1997). In addition to the management practices mentioned above, veterinary hygienic measures, or good production practices (GMPs), represent "... the most important ..." barrier to epidemics of veterinary infectious diseases. GMPs include proper: (1) hygiene of feed and water, (2) hygiene of air and climate, (3) husbandry and technology, (4) disposal of feces and sewage, (5) protection of the production unit against contamination from the environment, (6) cleaning and disinfection, and (7) all-in all-out systems (Martin, 1997).

Ban of Antibiotic Growth Promoters in Sweden

The total use of antibacterials in Sweden increased from 41.3 to 50.6 tons from 1980 to 1984 (Wierup, 1997). Requirements for a veterinary prescription for all antibacterials was introduced in 1986. Subsequently, the total use of antibacterials decreased by 49% from 50.6 tons in 1984 to 24.8 tons in 1986. By 1996, consumption of the active ingredients had decreased by 55% from the pre-ban (i.e., 1985) levels of consumption.

Is antimicrobial-free livestock production possible? Antibiotics for growth-promoting purposes have been banned in Sweden starting in 1986 (Wierup, 1997). Immediate attempts to improve the animal production environment were made in connection with this ban. A national standard for environmental improvement was created by poultry producers, and this standard became a target for which all poultry production units were to strive. Virginiamycin was used commonly prior to the 1986 ban on using this drug to prevent necrotic enteritis. Its use was continued during the transition period immediately after the ban (i.e., through 1987), suggesting the AGP ban in Sweden actually began in 1988, not 1986 (Wierup, 1997). Phenoxymethyl penicillin, an alternative to virginiamycin, was used first in 1987. The amount of active antibiotic ingredients in two commonly used antibiotics, virginiamycin and phenoxymethyl penicillin, decreased from 1,818 kg in 1987 (virginiamycin) to 100 kg in 1988 (phenoxymethyl penicillin). Since 1995, virtually no antibiotics have been used in Sweden against necrotic enteritis in poultry.

Because antibiotics are effective growth promoters, it can be hypothesized that a ban on antibiotics would lead to decreased productivity (e.g., reduced growth rates). Two negative effects on productivity of the Swedish ban in "1986" were: (1) increased the age-to-30 kg bodyweight by 2.0 days in pigs, (2) increased problems with necrotic enteritis in broilers, initially. Three un-altered effects of the Swedish ban in "1986" were: (1) did not decrease egg production in layers, (2) did not decrease growth rate in turkeys, (3) no reports of decreased productivity in specialized beef production. In conclusion, the Swedish Animal Health Service concluded that a ban on growth promoters provides evidence that poultry, calves, and pigs can be reared without continuous use of growth promoters, if the benefits of other production practices such as hygiene are maximized (Wierup, 1997). If the production data reported here were collected prior to 1988, they should be interpreted cautiously, since the true ban on all AGPs did not begin until 1988.

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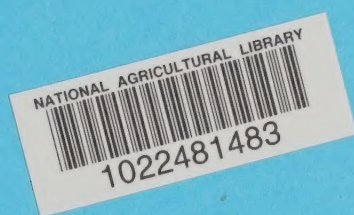
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